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TO: Rebecca Cook
Location: CM1/2B07&2D01
Art Unit: 1614
Wednesday, November 26, 2003
Case Serial Number: 09/962286
26

From: Paul Schulwitz
Location: Biotech-Chem Library
CM1-6B06
Phone: 305-1954

paul.schulwitz@uspto.gov

Search Notes

Examiner Cook,

See attached results.

If you have any questions about this search feel free to contact me at any time.

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Part I

FILE 'HCAPLUS' ENTERED AT 15:49:08 ON 26 NOV 2003
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FILE COVERS 1907 - 26 Nov 2003 VOL 139 ISS 22
FILE LAST UPDATED: 25 Nov 2003 (20031125/ED)

This file contains CAS Registry Numbers for easy and accurate
substance identification.

```
=> d que l4
L1            11 SEA FILE=REGISTRY ABB=ON  PLU=ON  .ALPHA.-LIPOIC ACID?/CN
L2           551 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L1(L)(BAC OR DMA OR PAC OR
                 PKT OR THU)/RL
L3        165198 SEA FILE=HCAPLUS ABB=ON  PLU=ON  ANTITUMOR AGENTS+OLD/CT
L4            31 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L2 AND L3

=> d que l5
L1            11 SEA FILE=REGISTRY ABB=ON  PLU=ON  .ALPHA.-LIPOIC ACID?/CN
L2           551 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L1(L)(BAC OR DMA OR PAC OR
                 PKT OR THU)/RL
L5             4 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L2 AND METASTAS?

=> d que l6
L1            11 SEA FILE=REGISTRY ABB=ON  PLU=ON  .ALPHA.-LIPOIC ACID?/CN
L2           551 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L1(L)(BAC OR DMA OR PAC OR
                 PKT OR THU)/RL
L6             4 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L2 AND CELL?(3A)ADHES?

=> s l4 or l5 or l6
L51           35 L4 OR L5 OR L6

=> b medline
FILE 'MEDLINE' ENTERED AT 15:49:45 ON 26 NOV 2003

 FILE LAST UPDATED: 25 NOV 2003 (20031125/UP). FILE COVERS 1958 TO DATE.

 On April 13, 2003, MEDLINE was reloaded. See HELP RLOAD for details.

 MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the
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MeSH 2003 vocabulary. See http://www.nlm.nih.gov/mesh/changes2003.html for a description on changes.

This file contains CAS Registry Numbers for easy and accurate substance identification.

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=> d que l15
L1           11 SEA FILE=REGISTRY ABB=ON  PLU=ON  .ALPHA.-LIPOIC ACID?/CN
L10         291 SEA FILE=MEDLINE ABB=ON  PLU=ON  L1
L11       80505 SEA FILE=MEDLINE ABB=ON  PLU=ON  ANTINEOPLASTIC AGENTS/CT
L13        1299 SEA FILE=MEDLINE ABB=ON  PLU=ON  THIOCTIC ACID/CT
L15           6 SEA FILE=MEDLINE ABB=ON  PLU=ON  (L10 OR L13) AND L11


=> d que l16
L1           11 SEA FILE=REGISTRY ABB=ON  PLU=ON  .ALPHA.-LIPOIC ACID?/CN
L10         291 SEA FILE=MEDLINE ABB=ON  PLU=ON  L1
L13        1299 SEA FILE=MEDLINE ABB=ON  PLU=ON  THIOCTIC ACID/CT
L16           1 SEA FILE=MEDLINE ABB=ON  PLU=ON  (L10 OR L13) AND METASTAS?


=> d que l17
L1           11 SEA FILE=REGISTRY ABB=ON  PLU=ON  .ALPHA.-LIPOIC ACID?/CN
L10         291 SEA FILE=MEDLINE ABB=ON  PLU=ON  L1
L13        1299 SEA FILE=MEDLINE ABB=ON  PLU=ON  THIOCTIC ACID/CT
L17           6 SEA FILE=MEDLINE ABB=ON  PLU=ON  (L10 OR L13) AND CELL?(3A)ADHE
                S?


=> s l15 or l16 or l17
L52          13 L15 OR L16 OR L17

=> b embase
FILE 'EMBASE' ENTERED AT 15:50:15 ON 26 NOV 2003
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 FILE COVERS 1974 TO 20 Nov 2003 (20031120/ED)

 EMBASE has been reloaded. Enter HELP RLOAD for details.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

=> d que l25
L1           11 SEA FILE=REGISTRY ABB=ON  PLU=ON  .ALPHA.-LIPOIC ACID?/CN
L22        1570 SEA FILE=EMBASE ABB=ON  PLU=ON  THIOCTIC ACID/CT
L23        1661 SEA FILE=EMBASE ABB=ON  PLU=ON  (L1 OR L22)
L24       52028 SEA FILE=EMBASE ABB=ON  PLU=ON  ANTINEOPLASTIC AGENT/CT
L25           9 SEA FILE=EMBASE ABB=ON  PLU=ON  L23 AND L24


=> d que l27
L1           11 SEA FILE=REGISTRY ABB=ON  PLU=ON  .ALPHA.-LIPOIC ACID?/CN
L22        1570 SEA FILE=EMBASE ABB=ON  PLU=ON  THIOCTIC ACID/CT
L23        1661 SEA FILE=EMBASE ABB=ON  PLU=ON  (L1 OR L22)
L26       53893 SEA FILE=EMBASE ABB=ON  PLU=ON  METASTASIS/CT
L27           1 SEA FILE=EMBASE ABB=ON  PLU=ON  L23 AND L26
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=> d que l38
L35          3234 SEA FILE=EMBASE ABB=ON  PLU=ON  METASTAS? AND CELL?(3A)ADHES?
L38             9 SEA FILE=EMBASE ABB=ON  PLU=ON  L35 AND BASAL?(3A)MEMBRANE


=> s l25 or l27 or l38
L53            19 L25 OR L27 OR L38

=> b biosis drugu ipa wpix
FILE 'BIOSIS' ENTERED AT 15:58:50 ON 26 NOV 2003
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FILE 'WPIX' ENTERED AT 15:58:50 ON 26 NOV 2003
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=> d que l42
L1             11 SEA FILE=REGISTRY ABB=ON  PLU=ON  .ALPHA.-LIPOIC ACID?/CN
L39          2836 SEA L1 OR THIOCTIC ACID OR LIPOIC ACID
L42             7 SEA L39 AND METASTAS?


=> d que l43
L1             11 SEA FILE=REGISTRY ABB=ON  PLU=ON  .ALPHA.-LIPOIC ACID?/CN
L39          2836 SEA L1 OR THIOCTIC ACID OR LIPOIC ACID
L43            16 SEA L39 AND CELL?(3A) ADHES?


=> s l42 or l43
L54            23 L42 OR L43

=> dup rem l52 l51 l53 l54
FILE 'MEDLINE' ENTERED AT 15:59:26 ON 26 NOV 2003

FILE 'HCAPLUS' ENTERED AT 15:59:26 ON 26 NOV 2003
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FILE 'DRUGU' ENTERED AT 15:59:26 ON 26 NOV 2003
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FILE 'WPIX' ENTERED AT 15:59:26 ON 26 NOV 2003
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PROCESSING COMPLETED FOR L52
PROCESSING COMPLETED FOR L51
PROCESSING COMPLETED FOR L53
PROCESSING COMPLETED FOR L54
L55 80 DUP REM L52 L51 L53 L54 (10 DUPLICATES REMOVED)

=> d ibib ab l55 1-80

L55 ANSWER 1 OF 80 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2003:133074 HCAPLUS
DOCUMENT NUMBER: 138:175883
TITLE: High molecular weight, lipophilic, orally ingestible bioactive agents in formulations having improved bioavailability
INVENTOR(S): Tao, Kar Wai C.; Yu, Ping; Roberts, Richard L.
PATENT ASSIGNEE(S): Shaklee Corporation, USA
SOURCE: PCT Int. Appl., 36 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003013566	A1	20030220	WO 2002-US19307	20020618
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2003044474	A1	20030306	US 2002-80975	20020221

PRIORITY APPLN. INFO.: US 2001-310151P P 20010803
US 2002-80975 A 20020221

AB Orally ingestible bioactive agents are disclosed which contain a triglyceride matrix and one or more polyphenols that improve the bioavailability of the bioactive agent. In particular non-limiting examples, the bioactive agent is a ubiquinone, such as Coenzyme Q, the triglyceride matrix is a soybean oil matrix, and the compn. further includes addnl. anti-oxidants. A soft gel capsule contg. a blend of a soybean oil matrix (GelOil SC) 317, coenzyme Q10 30 mg , Polygonum cuspidatum ext. contg. resveratrol and polyphenols 640 .mu.g, and mixed tocopherol 10 mg was formulated, and examd. the bioavailability.

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L55 ANSWER 2 OF 80 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2003:532331 HCAPLUS
DOCUMENT NUMBER: 139:79131
TITLE: Composition and method for treatment of neoplastic diseases associated with elevated matrix metalloproteinase activities using catechin compounds

INVENTOR(S): Netke, Shrirang; Ivanov, Vadim; Roomi, Waheed M.; Niedzwiecki, Aleksandra; Rath, Matthias
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 15 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003130201	A1	20030710	US 2002-41427	20020108
WO 2003057211	A1	20030717	WO 2002-EP1005	20020131

W: AE, AU, BR, CA, CN, CU, CZ, EE, HR, HU, ID, IL, IN, JP, KR, LT, LV, MK, MX, NO, NZ, OM, PH, PL, RO, RU, SG, SI, SK, TN, TR, UA, ZA, ZM
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR

PRIORITY APPLN. INFO.: US 2002-41427 A 20020108
AB The present invention relates to the use of catechin compds. in combination with other dietary constituents in inhibiting matrix-metalloproteinases. More particularly, the present invention relates to the use of a compn. comprising catechin, ascorbic acid, lysine and proline in treating neoplastic diseases.

L55 ANSWER 3 OF 80 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2003:174226 HCAPLUS
DOCUMENT NUMBER: 138:226702
TITLE: Oligo(ethylene glycol)-terminated 1,2-dithiolanes and their conjugates useful for preparing self-assembled monolayers
INVENTOR(S): Nelson, Deanna Jean
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 14 pp., Cont.-in-part of U.S. Ser. No. 946,023.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003044402	A1	20030306	US 2002-115558	20020403
US 2003059865	A1	20030327	US 2001-946023	20010905
WO 2003079403	A2	20030925	WO 2002-US25961	20020905

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR,

NE, SN, TD, TG
PRIORITY APPLN. INFO.: US 2001-946023 A2 20010905
US 2002-115558 A 20020403

AB The present invention provides biotechnol. useful oligo(ethylene glycol)-terminated 1,2-dithiolane compns. I [wherein n = 2-6; OEG = (OCH2CH2)x or is a branched oligoether; x = 2-100; L = N, O, S, P, amide, or hydrazide; Z = physiol. active therapeutic agent which has the ability to interact with biol. membranes] and conjugates of these compns. with biol. or nonbiol. receptor, ligand, sequestering, or reporter moieties. The invention also provides methods for the prepn. of these compns. (no data). Further, the invention provides self-assembled monolayer (SAM) compns. on a metal, e.g. gold, and methods for their prepn. (no data).

L55 ANSWER 4 OF 80 WPIX COPYRIGHT 2003 THOMSON DERWENT on STN
ACCESSION NUMBER: 2003-256330 [25] WPIX
DOC. NO. CPI: C2003-066379
TITLE: Treating disease e.g. atherosclerosis, Alzheimer's disease, diabetes, restenosis and anxiety comprises administering tetracycline compound.
DERWENT CLASS: B05
INVENTOR(S): DRAPER, M; JONES, G; LEVY, S B; NELSON, M L
PATENT ASSIGNEE(S): (PARA-N) PARATEK PHARM INC
COUNTRY COUNT: 99
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2003005971	A2	20030123	(200325)*	EN	79

RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG UZ VN YU ZA ZM ZW

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2003005971	A2	WO 2002-US22451	20020715

PRIORITY APPLN. INFO: US 2002-305546 20020712; US 2001-305546P 20010713

AB WO2003005971 A UPAB: 20030703
NOVELTY - Treating a disease comprises administering a tetracycline compound (I).
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:
(1) a composition comprising (I) and a second therapeutic agent, and
(2) a packaged composition comprising (I) and directions for using it.
ACTIVITY - Antiinflammatory; Antiarteriosclerotic; Cytostatic; Antidiabetic; Vasotropic; Protozoacide; Neuroprotective; Osteopathic; Antiarthritic; Antirheumatic; Cerebroprotective; Vulnerary; Antiulcer; Antiasthmatic; Hepatotropic; Virucide; Nootropic; Antiparkinsonian; Anticonvulsant; Neuroleptic; Hypotensive; Antidepressant; Antimanic;

Tranquilizer; Antimigraine; Antibacterial; Fungicide.

In an in vitro antibacterial assay, a compound of formula (Ia) exhibited minimum inhibitory concentration values of upto 4 mu g/ml against gram positive Staphylococcus aureus (RN450) and gram negative Escherichia coli (ML308225) bacteria.

MECHANISM OF ACTION - Protein glycosylation inhibitor.

USE - Used for treating inflammatory process associated states (IPAS), particularly acute lung injury, adult respiratory distress syndrome, acute respiratory distress syndrome, aortic or vascular aneurysm of vascular tissue (such as artery), arteriosclerosis, atherosclerosis, bone or cartilage degradation, bronchiectasis, cancer, chronic obstructive pulmonary disease, corneal ulceration, cystic fibrosis, dry eye, emphysema, ischemia and restenosis, nitric oxide associated states, particularly malaria, senescence, diabetes and vascular stroke, neurological disorders, particularly Alzheimer's disease, dementia, Parkinson's disease, Lewy diffuse body disease, senile dementia, Huntington's disease, Gilles de la Tourette's syndrome, multiple sclerosis, amyotrophic lateral sclerosis (ALS), progressive supranuclear palsy, epilepsy, Creutzfeldt-Jakob disease, an autonomic function disorder, hypertension, a sleep disorder, a neuropsychiatric disorder, depression, schizophrenia, schizoaffective disorder, Korsakoff's psychosis, mania, anxiety disorders, a phobic disorder, a learning disorder, a memory disorder, amnesia, age-related memory loss, attention deficit disorder, dysthymic disorder, major depressive disorder, obsessive-compulsive disorder, psychoactive substance use disorders, panic disorder, bipolar affective disorder, BP-1, migraine, traumatic brain injury, spinal cord trauma, motor neuron disease and nerve damage), matrix metalloproteinase state (particularly MMP-1, MMP-2, MMP-3, MMP-4, MMP-5, MMP-6, MMP-7, MMP-8, MMP-9, MMP-10, MMP-11, MMP-12, MMP-13, MMP-14, MMP-15, MMP-16, MMP-17, MMP-18, MMP-19 or MMP-20), **metastasis**, osteoarthritis, bone mass disorder (e.g. osteoporosis), osteosarcoma, osteomyelitis, periodontitis, rheumatoid arthritis, neurological disorders, skin and eye diseases, stroke, tissue wounds, tumor growth, tumor invasion, ulcerative colitis, chronic or recurrent inflammatory disorder and acute inflammatory disorder, chronic or recurrent lung disorder (e.g. asthma, emphysema, bronchitis and cystic fibrosis), hepatitis, sinusitis and angiogenesis and for inhibiting tumor **metastasis** (e.g. carcinoma and sarcoma) (all claimed).

Dwg.0/0

L55 ANSWER 5 OF 80 MEDLINE on STN

ACCESSION NUMBER: 2003282792 MEDLINE

DOCUMENT NUMBER: 22694378 PubMed ID: 12810681

TITLE: Dykellic acid inhibits phorbol myristate acetate-induced matrix metalloproteinase-9 expression by inhibiting nuclear factor kappa B transcriptional activity.

AUTHOR: Woo Ju-Hyung; Park Jong-Wook; Lee Sung-Hee; Kim Young-Ho; Lee In Kyu; Gabrielson Edward; Lee Sang-Han; Lee Ho-Jae; Kho Yung-Hee; Kwon Taeg Kyu

CORPORATE SOURCE: Department of Immunology, School of Medicine, Keimyung University, Taegu 700-712, Korea.

SOURCE: CANCER RESEARCH, (2003 Jun 15) 63 (12) 3430-4. Journal code: 2984705R. ISSN: 0008-5472.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200307
ENTRY DATE: Entered STN: 20030618
Last Updated on STN: 20030729
Entered Medline: 20030728

AB Proteolytic degradation of the extracellular matrix and tumor **metastasis** correlate with expression of endopeptidases known as matrix metalloproteinases (MMPs). Expression of MMPs is regulated by cytokines and signal transduction pathways, including those activated by phorbol myristate acetate. We found that dykellic acid, a fungal metabolite, significantly inhibits the phorbol myristate acetate-induced increase in MMP-9 expression and activity. These effects of dykellic acid are time- and dose-dependent, and correlate with decreased MMP-9 promoter activity and mRNA expression. Whereas this compound does not affect DNA binding activity of nuclear factor kappa B (NF kappa B), dykellic acid does inhibit transactivation of NF kappa B. These data demonstrate a role for NF kappa B in the regulation of MMP-9 expression and the ability of dykellic acid to suppress this action of NF kappa B.

L55 ANSWER 6 OF 80 DRUGU COPYRIGHT 2003 THOMSON DERWENT on STN
ACCESSION NUMBER: 2003-34765 DRUGU P V
TITLE: Use of DNA arrays to identify common molecular targets of chemopreventive angiogenesis inhibitors.
AUTHOR: Noonan D M; Pfeffer U; Benelli R; Tosetti F; Morini M; Ferrari N; Albini A
CORPORATE SOURCE: Nat.Inst.Cancer-Res.Genoa
LOCATION: Genoa, It.
SOURCE: Proc.Am.Assoc.Cancer Res. (94 Meet., 692-93, 2003) ISSN : 0197-016X
AVAIL. OF DOC.: Instituto Nazionale per la Ricerca sul Cancro, Genoa, Italy.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature

AB The effects of N-acetylcysteine, epigallocatechin-3-gallate, alpha-**lipoic acid** (thioctate) and fenretinide on gene expression were studied in human umbilical vein endothelial cells in-vitro using DNA arrays. None of the angiogenesis inhibitors had marked effects on gene expression but all 3 antioxidants regulated a subset of genes related to **cell** migration, **adhesion** or other process related to angiogenesis. The effect of fenretinide was similar, but clearly differed from that of the antioxidants. The method allows the molecular classification of antiangiogenic drugs and the determination of markers for their chemopreventive actions. (conference abstract: 94th Annual Meeting of the American Association for Cancer Research, 2003). (No EX).

L55 ANSWER 7 OF 80 EMBASE COPYRIGHT 2003 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2003224857 EMBASE
TITLE: Prophylactic effect of lipoic acid against adriamycin-induced peroxidative damages in rat kidney.
AUTHOR: Malarkodi K.P.; Balachandar A.V.; Sivaprasad R.; Varalakshmi P.
CORPORATE SOURCE: Dr. P. Varalakshmi, Department of Medical Biochemistry, PGIBMS, University of Madras, Taramani, Chennai 600 113, India. drvlakshmi@yahoo.com
SOURCE: Renal Failure, (2003) 25/3 (367-377).

Refs: 46
ISSN: 0886-022X CODEN: REFAE8
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 028 Urology and Nephrology
029 Clinical Biochemistry
037 Drug Literature Index
052 Toxicology
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Adriamycin (ADR), which is widely used in the treatment of various neoplastic conditions, exerts toxic effects in many organs. The present study was designed to investigate the effect of lipoic acid (LA) against acute ADR induced peroxidative damages in rat kidney. The study was carried out with adult male albino rats of Wistar strain, which comprised of one control and three experimental groups. Group I rats served as controls. Group II rats received ADR (7.5 mg/kg body weight) intravenously through the tail vein. Group III rats were given LA (75 mg/kg body weight) intraperitoneally. Group IV rats were given LA one day before the administration of ADR. Rats subjected to ADR administration showed a decline in the thiol capacity of the cell accompanied by high malondialdehyde (MDA) levels along with lowered activities of catalase (CAT), superoxide dismutase (SOD), glutathione peroxidase (GPx) glutathione (GSH) and GSH metabolizing enzymes (glutathione reductase (GR), glucose-6-phosphate dehydrogenase (G6PD)). However no significant change was observed in the activity of glutathione-S-transferees (GST). Pretreatment with LA showed considerable changes over oxidative stress parameters. Nephrotoxic damage was evident from the decrease in the activities of .gamma.-glutamyl transferase (.gamma.-GT) and .beta.-glucuronidase (.beta.-GLU), which were reverted upon LA pretreatment. Conclusion. This study has highlighted the beneficial effects of LA pretreatment in reversing the damages caused by ADR, by bringing about an improvement in the reductive status of the cell.

L55 ANSWER 8 OF 80 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2003:116192 HCAPLUS
DOCUMENT NUMBER: 139:46610
TITLE: .alpha.-Lipoic acid induces p27Kip-dependent cell cycle arrest in non-transformed cell lines and apoptosis in tumor cell lines
AUTHOR(S): Van De Mark, Karyn; Chen, James S.; Steliou, Kosta; Perrine, Susan P.; Faller, Douglas V.
CORPORATE SOURCE: Cancer Research Center, Boston University School of Medicine, Boston, MA, 02118, USA
SOURCE: Journal of Cellular Physiology (2003), 194(3), 325-340
CODEN: JCLLAX; ISSN: 0021-9541
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB .alpha.-Lipoic acid is a naturally occurring co-factor found in a no. of multi-enzyme complexes regulating metab. We report here that .alpha.-lipoic acid induces hyperacetylation of histones in vivo and has differential effects on the growth and viability of normal vs. transformed cell lines. The human tumor cell lines FaDu and Jurkat, as well as a Ki-v-Ras-transformed Balb/c-3T3 murine mesenchymal cell line, all initiated apoptosis following exposure to .alpha.-lipoic acid. In contrast, treatment of non-transformed cell lines with .alpha.-lipoic acid

resulted only in reversible cell cycle arrest in G0/G1. Treatment with butyrate, another short-chain fatty acid, induced a G0/G1 arrest in both transformed and non-transformed cell lines. .alpha.-Lipoic acid caused a post-translational elevation in the levels of the cyclin-dependent kinase inhibitor p27Kip1. Studies using p27Kip1-deficient MEF cells demonstrated that p27Kip1 was required for the .alpha.-lipoic acid-mediated cell cycle arrest. The mechanism of apoptosis was independent of Fas-mediated signaling, as .alpha.-lipoic acid-treated Jurkat cell mutants deficient in Fas or FADD retained sensitivity to apoptosis. The differential selectivity of the pro-apoptotic effects of .alpha.-lipoic acid for transformed cells supports its potential use in the treatment of neoplastic disorders.

REFERENCE COUNT: 78 THERE ARE 78 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L55 ANSWER 9 OF 80 EMBASE COPYRIGHT 2003 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2003215987 EMBASE
TITLE: Protective role of DL.alpha.-lipoic acid against adriamycin-induced cardiac lipid peroxidation.
AUTHOR: Balachandar A.V.; Malarkodi K.P.; Varalakshmi P.
CORPORATE SOURCE: P. Varalakshmi, Department of Medical Biochemistry, PGIBMS, University of Madras, Taramani Campus, Chennai 600 113, India. drvlakshmi@yahoo.com
SOURCE: Human and Experimental Toxicology, (1 May 2003) 22/5 (249-254).
Refs: 51
ISSN: 0960-3271 CODEN: HETOEA
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
030 Pharmacology
037 Drug Literature Index
052 Toxicology
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The cytoprotective activity of .alpha.-lipoic acid against free radical toxicity manifested during adriamycin (ADR)-induced cardiotoxicity has been investigated. ADR is a potent antitumour drug known to cause severe cardiotoxicity. Although ADR generates free radicals, the role of these radicals in the development of cardiac toxicity is still not well understood. In the present study, we evaluated the influence of chronic ADR treatment on the cellular defence mechanism against free radicals and the effect of .alpha.-lipoic acid supplementation on ADR-induced cardiotoxicity in male Wistar rats. The increase in lipid peroxidation (LPO) and activities of serum myocardial enzymes, namely lactate dehydrogenase (LDH) and creatinephosphokinase, associated with the decrease in activities of enzymatic (SOD, CAT, GPx, G6PD and GR) and non-enzymatic (GSH, Vit C and Vit E) antioxidants levels were the salient features observed in ADR-induced cardiotoxicity. Lipoic acid pretreated groups showed significant increase in activities of both enzymatic and non-enzymatic antioxidant levels. These observations highlight the antioxidant property of .alpha.-lipoic acid and its cytoprotective action against ADR-induced cardiotoxicity.

L55 ANSWER 10 OF 80 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2003:98500 HCAPLUS

DOCUMENT NUMBER: 138:248104
TITLE: The impact of different antioxidant agents alone or in combination on reactive oxygen species, antioxidant enzymes and cytokines in a series of advanced cancer patients at different sites: Correlation with disease progression
AUTHOR(S): Mantovani, Giovanni; Maccio, Antonio; Madeddu, Clelia; Mura, Loredana; Gramignano, Giulia; Lusso, Maria Rita; Murgia, Viviana; Camboni, Paolo; Ferreli, Luca; Mocci, Miria; Massa, Elena
CORPORATE SOURCE: Department of Medical Oncology, University of Cagliari, Cagliari, Italy
SOURCE: Free Radical Research (2003), 37(2), 213-223
CODEN: FRARER; ISSN: 1071-5762
PUBLISHER: Taylor & Francis Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In the present study we tested the ability of different antioxidant agents, used alone or in combination, to reduce the reactive oxygen species (ROS) levels and to increase the glutathione peroxidase (GPx) activity. Moreover, we tested the ability of such antioxidant agents to reduce the serum levels of proinflammatory cytokines IL-6 and TNF.alpha.. Fifty-six advanced stage cancer patients with tumors at different sites were included in the study: they were mainly stage III (12.5%) and stage IV (82.1%). The study was divided into two phases. In the 1st phase 28 patients were divided into five groups and a single different antioxidant agent was administered to each group. The selected antioxidant agents were: alpha lipoic acid or carboxycysteine-lysine salt, amifostine, reduced glutathione, vitamin A plus vitamin E plus Vitamin C. In the 2nd phase of the study 28 patients were divided into five groups and a combination of two different antioxidant agents was administered to each group. The antioxidant treatment was administered for 10 consecutive days. The patients were studied at baseline and after antioxidant treatment. Our results show that all single antioxidants tested were effective in reducing the ROS levels and three of them in increasing GPx activity, too. Among the combinations of antioxidant agents, three were effective in reducing ROS, while three were effective in increasing GPx activity (arm 4 was effective in both instances). Comprehensively, the "antioxidant treatment" was effective both on ROS levels and GPx activity. Moreover, the antioxidant treatment was able to reduce serum levels of IL-6 and TNF.alpha.. Furthermore, a correlation was shown between the Eastern Cooperative Oncol. Group Performance Status of patients and blood levels of ROS, GPx activity, serum levels of proinflammatory cytokines.
REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L55 ANSWER 11 OF 80 EMBASE COPYRIGHT 2003 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2003402598 EMBASE
TITLE: Subcutaneous interleukin-2 in combination with medroxyprogesterone acetate and antioxidants in advanced cancer responders to previous chemotherapy: Phase II study evaluating clinical, quality of life, and laboratory parameters.
AUTHOR: Mantovani G.; Madeddu C.; Gramignano G.; Lusso M.R.; Mocci M.; Massa E.; Ferreli L.; Astara G.; Maccio A.; Serpe R.
CORPORATE SOURCE: Prof. G. Mantovani, Cattedra e Div. di Oncologia Medica,

Policlin. Universitario di Cagliari, Presidio di Monserrato, Strada Statale 554, bivio Sestu, 09042 Monserrato, Cagliari, Italy. mantovan@pacs.unica.it

SOURCE: Journal of Experimental Therapeutics and Oncology, (2003) 3/4 (205-219).
Refs: 57
ISSN: 1359-4117 CODEN: JETOFX
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
017 Public Health, Social Medicine and Epidemiology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English

AB We carried out an open, non-randomized phase II study including all patients treated with whatever chemotherapy or combined modality regimen for whatever cancer who were in clinical objective response (complete response, CR, or partial response, PR) or stable disease (SD). The treatment consisted of administration of recombinant interleukin-2 (rIL-2) at a dose of 1.8 MIU subcutaneously three times/week (every other day) for the first 2 weeks of every month plus medroxyprogesterone acetate (MPA) 500 mg/day every other day plus antioxidant agents alpha-lipoic acid 300 mg/day and N-acetyl cysteine 1800 mg/day or carbocysteine lysine salt oral solution 2.7 g/day. The treatment was administered for 1 year except when progression of disease occurred. The primary study endpoints were to define clinical outcome, i.e. duration of response, survival (overall survival, OS and progression-free survival, PFS), the toxicity profile, and the evaluation of quality of life (QL). As secondary endpoints, we measured the changes of lymphocyte count, serum levels of proinflammatory cytokines, IL-2, C-reactive protein (CRP) and leptin, blood levels of reactive oxygen species (ROS) and antioxidant enzymes (glutathione peroxidase, GPx and superoxide dismertase, SOD). From July 1998 to June 2003, 42 patients were enrolled in the study (M/F ratio, 39/3; mean age, 62.5 years). Twenty (47.6%) patients were elderly (>65 years). The majority of patients had either head and neck cancer or lung cancer, 88% had locally advanced or metastatic disease at diagnosis, and 76% had ECOG 0. Forty patients were previously treated with chemotherapy (27 also with radiotherapy), two with IL-2 and interfiron (IFN), one with endocrine therapy and one with only surgery. We obtained an objective response to maintenance treatment of 50%. Median duration of response was 19 months and median PFS was 33 months. Median duration of maintenance treatment was 12 months, median follow-up duration from diagnosis to June 2003 was 40 months, and median follow-up duration from study entry to June 2003 was 17 months. The median overall survival has not been reached. Toxicity was negligible. As for QL, a significant improvement of cognitive functions was observed, whereas all other functioning and symptom scales did not change significantly. As for laboratory parameters, absolute lymphocyte count increased significantly, IL-6, IL-1.beta., tumor necrosis factor-.alpha., CRP, and fibrinogen decreased significantly whereas IL-2 and leptin increased significantly after treatment. ROS decreased significantly, whereas GPx increased significantly after treatment. Patients alive at study end showed a significant increase in absolute lymphocyte count, IL-2, leptin, and GPx and a significant decrease of proinflammatory cytokines, CRP, fibrinogen, and ROS, whereas patients who died before study end exhibited only a significant increase in absolute lymphocyte count, IL-2, and GPx and a significant decrease of ROS.

Long-term combined maintenance therapy with rIL-2 + MPA + antioxidant agents is feasible, has a very low toxicity, and results in the improvement of clinical outcome, QL, and laboratory parameters.

L55 ANSWER 12 OF 80 EMBASE COPYRIGHT 2003 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2003091340 EMBASE
TITLE: Basic and clinical researches on ototoxicity induced by platinum.
AUTHOR: Hara A.
SOURCE: Otolaryngology - Head and Neck Surgery (Tokyo), (2003) 75/2 (107-109).
Refs: 32
ISSN: 0914-3491 CODEN: JITGE2
COUNTRY: Japan
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 011 Otorhinolaryngology
016 Cancer
037 Drug Literature Index
038 Adverse Reactions Titles
052 Toxicology
LANGUAGE: Japanese

L55 ANSWER 13 OF 80 MEDLINE on STN
ACCESSION NUMBER: 2002400210 MEDLINE
DOCUMENT NUMBER: 22144307 PubMed ID: 12149316
TITLE: Effective treatment of oxaliplatin-induced cumulative polyneuropathy with alpha-lipoic acid.
AUTHOR: Gedlicka C; Scheithauer W; Schull B; Kornek G V
SOURCE: JOURNAL OF CLINICAL ONCOLOGY, (2002 Aug 1) 20 (15) 3359-61.
Journal code: 8309333. ISSN: 0732-183X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Letter
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200209
ENTRY DATE: Entered STN: 20020801
Last Updated on STN: 20020907
Entered Medline: 20020906

L55 ANSWER 14 OF 80 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2002:220551 HCAPLUS
DOCUMENT NUMBER: 136:246398
TITLE: Methods and compositions using antioxidant for reducing antibody-mediated generation of hydrogen peroxide and superoxide and oxidative stress
INVENTOR(S): Wentworth, Paul; Wentworth, Anita D.; Jones, Lyn H.; Janda, Kim D.; Lerner, Richard A.
PATENT ASSIGNEE(S): The Scripps Research Institute, USA
SOURCE: PCT Int. Appl., 103 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO. KIND DATE APPLICATION NO. DATE

WO 2002022573	A2	20020321	WO 2001-US29165	20010917
WO 2002022573	A3	20031002		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

AU 2002012970	A5	20020326	AU 2002-12970	20010917

PRIORITY APPLN. INFO.:	US 2000-232702P	P 20000915
	US 2000-235475P	P 20000926
	US 2001-315906P	P 20010829
	WO 2001-US29165	W 20010917

AB The invention relates to method of using antioxidant for reducing antibody-mediated generation of superoxide or hydrogen peroxide from singlet oxygen and oxidative stress. The antioxidant is ascorbic acid, .alpha.-tocopherol, .gamma.-glutamylcysteinylglycine, .gamma.-glutamyl transpeptidase, .alpha.-lipoic acid, dihydrolipoate, N-acetyl-5-methoxytryptamine, flavones, flavonenes, flavanols, catalase, peroxidase, superoxide dismutase, metallothionein, or butylated hydroxytoluene. The invented method is useful for treating diseases exhibiting oxidative stress, e.g. cancer, inflammatory disease, ischemic disease, hemochromatosis, acquired immunodeficiency syndrome, emphysema, organ transplant, gastric ulcer, hypertension, preeclampsia, neurol. disease, alcoholism and smoking-related diseases. Also provided are screening assays to identify agents that modulate the ability of a antibody to generate superoxide and hydrogen peroxide. Further, the invention provides methods to use antibodies in immunoassays.

L55 ANSWER 15 OF 80 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER:	2002:717053 HCAPLUS
DOCUMENT NUMBER:	137:226597
TITLE:	Combination and method of treatment of cancer utilizing a COX-2 inhibitor and a 3-hydroxy-3-methylglutaryl-coenzyme-a (HMG-CoA) reductase inhibitor
INVENTOR(S):	Kindness, George; Schumm, Brooke; Guilford, F. Timothy
PATENT ASSIGNEE(S):	USA
SOURCE:	U.S. Pat. Appl. Publ., 23 pp., Cont.-in-part of Appl. No. PCT/US01/31328. CODEN: USXXCO
DOCUMENT TYPE:	Patent
LANGUAGE:	English
FAMILY ACC. NUM. COUNT:	5

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002132781	A1	20020919	US 2001-997490	20011117
US 2002086894	A1	20020704	US 2001-912703	20010725
US 6534540	B2	20030318		
WO 2002028270	A2	20020411	WO 2001-US31328	20011006
WO 2002028270	A3	20020613		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT,
RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US,
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RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AM, AZ, BY, KG,
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IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN,
GQ, GW, ML, MR, NE, SN, TD, TG

WO 2002067853 A2 20020126 WO 2002-US2480 20020126

WO 2002067853 A3 20021031

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
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RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
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GN, GQ, GW, ML, MR, NE, SN, TD, TG

WO 2002083124 A1 20021024 WO 2002-US2478 20020126

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CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
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RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH,
CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR,
BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

WO 2002094021 A1 20021128 WO 2002-US2477 20020126

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT,
RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US,
UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH,
CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR,
BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.:

US 2000-238504P	P	20001006
US 2000-238506P	P	20001006
US 2000-243901P	P	20001027
US 2000-243902P	P	20001027
US 2000-245592P	P	20001103
US 2001-264511P	P	20010126
US 2001-307689P	P	20010725
US 2001-912703	P	20010725
WO 2001-US31328	W	20011006
US 2000-249592P	P	20001117
US 2001-263486P	P	20010123
US 2001-264504P	P	20010126
US 2001-997490	A2	20011117
US 2002-352047P	P	20020126

AB The inventors propose a combination of an HMG-CoA reductase inhibitor

(also referred to as "HMG-CoA inhibitor(s)"), and COX-2 inhibitor for the treatment of cancer esp. prostate cancer and a method of treatment of cancer by that combination, esp. prostate cancer. The inventors propose a combination of an HMG-CoA reductase inhibitor, COX-2 inhibitor, and glutathione pathway enhancing and detoxifying compd., particularly cystine, for the treatment of cancer esp. prostate cancer and a method of treatment of cancer by that combination, esp. prostate cancer. Also contemplated is the addn. of lipoic acid and compds. to maintain adequate levels of selenium, vitamin C and vitamin E. Based on the clin. results of retardation, but not cure of cancer, the combination has the characteristics of sufficiently interfering with replication and apparently restoring the immune system capacity to manage cancer.

L55 ANSWER 16 OF 80 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2002:143204 HCAPLUS
DOCUMENT NUMBER: 136:189383
TITLE: A water-free transdermal delivery system
INVENTOR(S): Dransfield, Charles William
PATENT ASSIGNEE(S): Australia
SOURCE: U.S. Pat. Appl. Publ., 17 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002022052	A1	20020221	US 2001-863764	20010524
PRIORITY APPLN. INFO.:			AU 2000-6691 A	20000406
			AU 2000-8885 A	20000721

AB A transdermal or transepithelial compn. substantially free of water comprises a biol. active agent in the form of microfined particles, sized less than 2 .mu. down to less than 0.1 .mu., which by massage pressure are mech. entrained within the interstices of the stratum corneum. Particles < 0.5 .mu. do not require a carrier for entrainment. Delivery into mucosal epithelia is obtained by particles < 1 .mu. with delivery increasing with decreasing particle size. For example, in order to demonstrate the present invention, two compns. contg. ibuprofen as the active agent were prepd. Particles in both samples were identical (< 0.5 .mu.m). However, sample A was water-free, while sample B contained 10% water. Transdermal absorption of the ibuprofen prepns. were compared using fresh bovine udder skin mounted on Franz diffusion cells at 37.degree.. Approx. 30 mg of the ibuprofen prepn. was applied to the skin and massaged into the skin using a vibratory massager. The water free sample (A) demonstrated a higher rate of absorption in less time than a similar formulation contg. 10% water (sample B). In sample B the delivery was more than halved and the time rate of the delivery was found to be greatly reduced with delivery curve showing 16% over 12 h and only a further 7.5% delivery over the next 12 h.

L55 ANSWER 17 OF 80 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2002:885974 HCAPLUS
DOCUMENT NUMBER: 137:375255
TITLE: Lipoic acid for suppressing undesired hematological effects of chemotherapy and/or radiotherapy
INVENTOR(S): Van Den Berg, Jeroen; Osanto, Susanne.; Hageman,

Robert
PATENT ASSIGNEE(S): N.V. Nutricia, Neth.
SOURCE: Eur. Pat. Appl., 10 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1258243	A1	20021120	EP 2001-201835	20010516
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
WO 2002092077	A2	20021121	WO 2002-NL315	20020516
WO 2002092077	A3	20030320		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				

PRIORITY APPLN. INFO.: EP 2001-201835 A 20010516

AB A method of suppressing the detrimental effects of chemotherapy and/or radiotherapy on a patient's blood cell count and health using lipoic acid and/or lipoic acid analog is described. A pharmaceutical or dietetic prepn. comprises lipoic acid and/or lipoic acid analog in an amt. equiv. to 40-2000 mg R(+)-lipoic acid, 0.2-60 .mu.m moles intact protein, 200-800 mg vitamin C, 100-500 mg vitamin D, 200-1000 mg N-acetyl cysteine, and 5-100 mg zinc.

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L55 ANSWER 18 OF 80 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2002:47521 HCAPLUS
DOCUMENT NUMBER: 136:96095
TITLE: Use of lipoic acid as a bioavailability enhancer for mineral salts
INVENTOR(S): Kramer, Klaus; Klatt, Martin Jochen
PATENT ASSIGNEE(S): BASF Aktiengesellschaft, Germany
SOURCE: Eur. Pat. Appl., 23 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1172110	A2	20020116	EP 2001-116197	20010704
EP 1172110	A3	20030917		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				

DE 10032601	A1	20020117	DE 2000-10032601	20000707
DE 10109303	A1	20021128	DE 2001-10109303	20010226
US 2002028796	A1	20020307	US 2001-897922	20010705
JP 2002121134	A2	20020423	JP 2001-207026	20010706
CN 1337228	A	20020227	CN 2001-125486	20010707

PRIORITY APPLN. INFO.: DE 2000-10032601 A 20000707
DE 2001-10109303 A 20010226

AB The invention discloses the use of .alpha.-lipoic acid or .alpha.-dihydrolipoic acid for increasing the bioavailability of mineral salts, as well as the use of .alpha.-lipoic acid or .alpha.-dihydrolipoic acid in combination with metal salts, esp. the use of metal .alpha.-lipoates, metal .alpha.-dihydrolipoates, and metal-.alpha.-lipoic acid complexes, esp. in mineral prepns. or medicaments, as well as the metal .alpha.-lipoates, metal .alpha.-dihydrolipoates and metal-.alpha.-lipoic acid complexes themselves. Prepn. of e.g. Zn[(R)-.alpha.-lipoate]2(H2O)2 is described.

L55 ANSWER 19 OF 80 WPIX COPYRIGHT 2003 THOMSON DERWENT on STN
ACCESSION NUMBER: 2002-722021 [78] WPIX
CROSS REFERENCE: 1994-007207 [01]; 1995-215069 [28]; 1995-224099 [29]; 1995-231267 [30]; 1995-231268 [30]; 1996-362013 [36]; 1997-296858 [27]; 1998-086536 [08]; 1999-059154 [05]; 2000-159953 [14]; 2000-440986 [38]; 2001-307383 [32]
DOC. NO. CPI: C2002-204234
TITLE: Delivering active agent to targeted in vivo site for treating cancer comprises administering conjugate comprising targeting group and member of ligand antiligand binding pair, administering clearing agent and administering second agent.
DERWENT CLASS: B05 B07
INVENTOR(S): AXWORTHY, D B; RENO, J M; THEODORE, L J
PATENT ASSIGNEE(S): (NEOR-N) NEORX CORP
COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
US 6416738	B1	20020709	(200278)*		93

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
US 6416738	B1	CIP of	US 1992-895588	19920609
		CIP of	US 1992-995381	19921223
		CIP of	WO 1993-US5406	19930607
		CIP of	US 1993-163184	19931207
		Cont of	US 1994-350551	19941207
			US 2000-561736	20000425

FILING DETAILS:

PATENT NO	KIND		PATENT NO
US 6416738	B1	CIP of	US 5283342
		Cont of	US 6075010

PRIORITY APPLN. INFO: US 1994-350551 19941207; US 1992-895588 19920609; US 1992-995381 19921223; WO 1993-US5406 19930607; US 1993-163184 19931207; US 2000-561736 20000425

AB US 6416738 B UPAB: 20030224

NOVELTY - Delivering an active agent to a targeted in vivo site comprises:

(a) administering a first conjugate comprising a targeting group and a member of a ligand/antiligand binding pair;

(b) administering a clearing agent directing the clearance of circulating first conjugate to the recipient and

(c) administering a second conjugate comprising an active agent and a ligand/antiligand binding pair member.

DETAILED DESCRIPTION - Delivering an active agent to a targeted in vivo site comprises:

(a) administering a first conjugate comprising a targeting group and a member of a ligand/antigen binding pair;

(b) administering a clearing agent directing the clearance of circulating first conjugate to the recipient, and

(c) administering a second conjugate comprising an active agent and a ligand/antiligand binding pair member.

The second conjugate binding pair member is complementary to that of the first conjugate. The clearing agent is a small molecule having a molecular weight of 1000-20000 Daltons which clears the in vivo first conjugate from the circulation via a hepatocyte receptor mediated clearance mechanism. The small molecule clearing agent comprises at least a ligand or antiligand that provides binding of the clearing agent to the complementary ligand or antiligand containing conjugate, to be cleared from the circulation or at least three covalently attached terminal hexose residues and spaced on the clearing agent molecule to enable the clearing agent to bind a hepatocyte receptor and provide hepatocyte receptor mediated clearance of the ligand or antiligand containing conjugate.

ACTIVITY - Cytostatic.

MECHANISM OF ACTION - None given in the source material.

USE - Used for delivering a targeting group that is conjugated to member of a ligand/antiligand pair (claimed), which is useful in diagnostic and therapeutic pretargeting, particularly for treating liver tumors, brain primary tumors and **metastases**, lung carcinomas and kidney carcinomas.

A 186-Re-chelate-biotin conjugate (MW 1000; specific activity = 1-2 mCi/mg) was examined in a three-step pretargeting protocol in an animal model. 18-22 g Female nude mice were implanted subcutaneously with LS-180 human colon tumor xenografts, yielding 100-200 mg tumors within 10 days of implantation. NR-LU-10 antibody (MW 150 kD) was radiolabeled with 125 I/Chloramine T and biotinylated via lysine residues. Avidin (MW 66 kD) was radiolabeled with 131I/PIP-NHS.

The experimental protocol was as follows: Group 1: Time 0, inject 100 mu g 125I-labeled, biotinylated NR-LU-10; Time 24 hour, inject 400 mu g 131I-labeled avidin; Time 26 hour, inject 60 mu g 186Re-chelate-biotin conjugate; Group 2 (control): Time 0, inject 400 mu g, 131I-labeled avidin Time 2 hour, inject 60 mu g 186Re-chelate-biotin conjugate, Group 3 (control): Time 0, inject 60 mu g 186Re-chelate biotin conjugate.

Results showed that the rate and 50 extent of avidin clearance were similar in the biotinylated antibody. The effect of biotinylated antibody and avidin on blood clearance of the 186Re-chelate-biotin conjugate was examined and blood clearance was similar in the presence or absence of biotinylated antibody and avidin. Antibody immunoreactivity was found to be uncompromised by biotinylation at the level tested.

The tumor uptake of biotinylated antibody administered at time 0 or of avidin administered at time 24 hour was examined. At 25 hour, 350 pmol/g biotinylated antibody was present at the tumor; at 32 hour the level was 300 pmol/g; at 48 hour, 200 pmol/g, and at 120 hour, 100 pmol/g. Avidin uptake at the same time points was 250, 150, 50 and 0 pmol/g, respectively. From the same experiment, 65 tumor to blood ratios were determined for biotinylated antibody and for avidin. From 32 - 120 hour, the ratios of tumor to blood were very similar. Rapid and efficient removal of biotinylated antibody from the blood by complexation with avidin was observed. Within two hours of avidin administration, a 10 times reduction in blood pool antibody concentration was obtained, resulting in a sharp increase in tumor to blood ratios. Avidin was cleared rapidly, with greater than 90% of the injected dose cleared from the blood within 1 hour after administration. The 186Re-biotin chelate was rapidly cleared, with greater than 99% of the injected dose cleared from the blood by 1 hour after administration.

ADVANTAGE - The method allows the localized delivery of the targeting and therapeutic groups, and avoids the binding of the radioisotope to unwanted sites such as bone marrow or circulation, causing administration of large doses of harmful radiation to these organs.
Dwg.0/25

L55 ANSWER 20 OF 80 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2002:535817 HCAPLUS
DOCUMENT NUMBER: 137:108069
TITLE: Phase II study of subcutaneously administered interleukin-2 in combination with medroxyprogesterone acetate and antioxidant agents as maintenance treatment in advanced cancer responders to previous chemotherapy
AUTHOR(S): Mantovani, Giovanni; Maccio, Antonio; Madeddu, Clelia; Mulas, Carlo; Massa, Elena; Astara, Giorgio; Ferreli, Luca; Mudu, Maria Caterina; Gramignano, Giulia; Murgia, Viviana; Lusso, Maria Rita; Mocci, Miria; Cardia, Alessandra; Mura, Loredana
CORPORATE SOURCE: Department of Medical Oncology, University of Cagliari, Carbonia, 09042, Italy
SOURCE: Oncology Reports (2002), 9(4), 887-896
CODEN: OCRPEW; ISSN: 1021-335X
PUBLISHER: Oncology Reports
DOCUMENT TYPE: Journal
LANGUAGE: English

AB An open, non-randomized phase II study was carried out including patients with advanced solid tumors who achieved an objective response or disease stabilization as a result of previous chemotherapy, to receive a maintenance treatment with recombinant interleukin-2 (rIL-2) plus medroxyprogesterone acetate (MPA) plus antioxidant agents alpha-lipoic acid (ALA) and N-acetyl cysteine (NAC). The first study endpoints were to define clin. outcome and toxicity as well as the evaluation of quality of life. As secondary endpoints we measured the changes of lymphocyte abs. count, the serum levels of proinflammatory cytokines, IL-2, C-reactive protein (CRP) and leptin after treatment. RIL-2 was administered at a dose of 1.8 MIU s.c. 3 times/wk on alternate days for the first two weeks of every month and MPA was given orally at a dose of 500 mg/day at alternate days without interruption. ALA 300 mg/day orally and NAC 1800 mg/day orally were also administered continuously. Twenty-eight patients were enrolled in the study. The median duration of maintenance treatment

was 10 mo (6-30+). The response to maintenance treatment at Sept. 15, 2001 was: CR 11 patients (39.3%); SD 2 patients (7.1%); PD 15 patients (53.6%). The median duration of response was 11 mo (6-34+). The median follow-up duration was 11 mo (6-34+). The median OS was not reached. The median PFS was 21.5 mo (1-40+). The 1-yr survival rate was 72.2%. At Sept. 15, 2001, 16 patients were still surviving. No grade 3/4 toxicity and one grade 2 skin toxicity were obsd. We found a significant increase of the abs. lymphocyte count and serum levels of IL-2 and a significant decrease of TNF.alpha. after treatment. The evaluation of patient subgroups showed the following: the patients alive at the end of study had a significant increase of lymphocyte count, IL-2 and leptin, and a significant decrease of IL-1.beta., IL-6 and TNF.alpha., whereas the patients who had died had only a significant increase of lymphocyte count and IL-2. Among the patients alive, those in objective clin. response (CR + PR) + those in SD had a significant increase of lymphocyte count, IL-2 and leptin and a significant decrease of IL-1.beta., IL-6 and TNF.alpha., whereas those with PD had no significant changes in any of the above values. We conclude that the combination of s.c. rIL-2 with oral MPA and anti-oxidant agents ALA and NAC in an rIL-2 with oral MPA and anti-oxidant agents ALA and NAC in an intermittent schedule, repeated for a long-term period, is feasible, has a very low toxicity and results in the improvement of biol. markers which are predictive for patient outcome. intermittent schedule, repeated for a long-term period, is feasible, has a very low toxicity and results in the improvement of biol. markers which are predictive for patient outcome.

REFERENCE COUNT: 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L55 ANSWER 21 OF 80 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2002:114713 HCAPLUS
DOCUMENT NUMBER: 137:57110
TITLE: Differential effects of the antioxidant .alpha.-lipoic acid on the proliferation of mitogen-stimulated peripheral blood lymphocytes and leukaemic T cells
AUTHOR(S): Pack, Robert A.; Hardy, Kristine; Madigan, Michele C.; Hunt, Nicholas H.
CORPORATE SOURCE: Department of Pathology, University of Sydney, Sydney, 2006, Australia
SOURCE: Molecular Immunology (2002), 38(10), 733-745
CODEN: MOIMD5; ISSN: 0161-5890
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The effects of the antioxidant .alpha.-lipoic acid (LA) on the proliferation of mitogen-stimulated human peripheral blood lymphocytes (HPBL) were investigated in comparison to its effects on the proliferation of two leukemic T cell lines, Jurkat and CCRF-CEM. At low mM concns., LA inhibited in a dose-dependent manner DNA synthesis of HPBL stimulated with either phorbol myristate acetate (PMA) in combination with ionomycin (IoM), or phytohemagglutinin (PHA). At similar concns., LA inhibited the proliferation of Jurkat and CCRF-CEM cells. However, LA was preferentially cytotoxic to the leukemic cell lines. The selective toxicity of LA to Jurkat cells was shown by electron microscopy (EM) to be due to the induction of apoptosis. Furthermore, LA had different effects on the secretion of interleukin-2 (IL-2) and steady-state levels of IL-2 mRNA in mitogen-stimulated HPBL depending on the mitogens used. LA dramatically increased the induction of IL-2 mRNA and IL-2 protein

secretion in PMA/IoM-stimulated HPBL, whereas it inhibited these in HPBL stimulated with PHA. The differential effects of LA on normal and leukemic T lymphocytes may indicate a new route towards development of therapeutic agents.

REFERENCE COUNT: 58 THERE ARE 58 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L55 ANSWER 22 OF 80 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2002:363923 HCAPLUS
DOCUMENT NUMBER: 137:15422
TITLE: Dose-intense phase II study of weekly cisplatin and epidoxorubicin plus medroxyprogesterone acetate and recombinant interleukin 2 in stage IIIB-IV non-small cell lung cancer
AUTHOR(S): Mantovani, Giovanni; Maccio, Antonio; Mulas, Carlo; Massa, Elena; Madeddu, Clelia; Mura, Loredana; Contu, Paolo; Versace, Renato
CORPORATE SOURCE: Departments of Medical Oncology, 'Sirai' Hospital, Carbonia, Italy
SOURCE: Oncology Reports (2002), 9(3), 661-670
CODEN: OCRPEW; ISSN: 1021-335X
PUBLISHER: Oncology Reports
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The purpose of the study was to evaluate the effectiveness in terms of response rates, toxicity and survival of the combination chemotherapy regimen cisplatin and epidoxorubicin (epirubicin) including medroxyprogesterone acetate (MPA), recombinant IL-2 (rIL-2) and antioxidants in patients with advanced (stage IIIB-IV) non-small cell lung cancer (NSCLC). Thirty-three chemotherapy-naive patients with NSCLC were enrolled in the study and 30 of them were evaluable. The mean age of the patients was 61 yr. Twenty (66.7%) out of 30 patients were .gtoreq.60 yr, and 5 (16.7%) patients were .gtoreq.70 yr. The ECOG performance status was 0 to 1 in 30 patients and 2 in 3 patients. Twenty-six patients (78.8%) had stage IIIB disease and 7 (21.2%) had stage IV; histol. was mainly squamous cell carcinoma (72.7%). The treatment consisted of cisplatin 40 mg/M2/wk and epirubicin 40 mg/ M2/wk both i.v. on day 1, rIL-2 1.8 MIU/day s.c., MPA 1 g/day orally, alpha-lipoic acid 300 mg/ day orally and N-acetyl cysteine 1.8 g/day orally. The treatment was administered for 6 wk. Patients with a complete response (CR), partial response (PR) or stable disease (SD) continued the treatment, according to response re-evaluation, until 15 wk. The present study reports the results of 6, 9, 12 and 15-wk treatment. After 6 wk, 30 patients were assessable for response: no CR was obsd., a PR was achieved in 15 patients (50%; ORR 50%). After 15 wk, 1 CR and 8 PR were obsd. (ORR 30.0%). The median follow-up period was 13 mo. The median duration of response was 9 mo. The median overall survival (OS) was 15 mo. The one-year survival rate was 55.8%. The median progression-free survival (PFS) was 10 mo. The toxicity was, as expected, mainly hematol.: neutropenia was the most significant symptom. The non-hematol. toxicity was quite low. Therefore, the treatment's toxicity was quite acceptable. There was no toxic death. The 30.0% ORR, the 15 mo OS and the 10 mo PFS obtained in this study are comparable with those obsd. with cisplatin plus epirubicin (ORR 39-54%) in phase II studies and in a previous phase III study (ORR 33%, OS 10.5 mo). Moreover, the toxicity was acceptable and it was mainly hematol. Serum levels of proinflammatory cytokines significantly decreased after treatment.

REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L55 ANSWER 23 OF 80 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2003:252867 HCAPLUS
DOCUMENT NUMBER: 139:317363
TITLE: Reactive oxygen species, antioxidant mechanisms and serum cytokine levels in cancer patients: impact of an antioxidant treatment
AUTHOR(S): Mantovani, G.; Maccio, A.; Madeddu, C.; Mura, L.; Massa, E.; Gramignano, G.; Lusso, M. R.; Murgia, V.; Camboni, P.; Ferreli, L.
CORPORATE SOURCE: Department of Medical Oncology, University of Cagliari, Cagliari, Italy
SOURCE: Journal of Cellular and Molecular Medicine (2002), 6(4), 570-582
CODEN: JCMMC9; ISSN: 1582-1838
PUBLISHER: "Carol Davila" University Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB So far, it is not well established whether oxidative stress found in cancer patients results from an increased prodn. of oxidants in the body or from a failure of physiol. antioxidant systems. To further investigate this question we have assessed the blood levels of reactive oxygen species as a marker of free radicals producing oxidative stress and the most relevant of the physiol. body enzymes counteracting reactive oxygen species, namely glutathione peroxidase and superoxide dismutase. Serum levels of proinflammatory cytokines and IL-2 were also investigated. All these parameters were studied in relation to the clin. most important index of disease progression, namely Performance Status (ECOG PS). We also tested the reducing ability of different antioxidant agents on reactive oxygen species levels by measuring the increase in glutathione peroxidase activity, and the redn. of serum levels of IL-6 and TNF. We carried out an open non randomized study on 28 advanced stage cancer patients (stage III, 10.7 %, and stage IV, 89.3%) with tumors at different (8) sites: all were hospitalized in the Medical Oncol. Dept, University of Cagliari Interventions. The patients were divided into 5 groups and a different antioxidant treatment was administered to each group. The selected antioxidants were: alpha lipoic acid 200 mg/day orally, N-acetylcysteine 1800 mg/day i.v. or carboxycysteine-lysine salt 2.7 g/day orally, amifostine 375 mg/day i.v., reduced glutathione 600 mg/day i.v., vitamin A 30000 IU/day orally plus vitamin E 70 mg/day orally plus Vitamin C 500 mg/day orally. The antioxidant treatment was administered for 10 consecutive days. Our results show that all but one of the antioxidants tested were effective in reducing reactive oxygen species levels and 2 of them (cysteine-contg. compds. and amifostine) had the addnl. effect of increasing glutathione peroxidase activity. Comprehensively, the "antioxidant treatment" was found to have an effect both on reactive oxygen species levels and glutathione peroxidase activity. The antioxidant treatment also reduced serum levels of IL-6 and TNF. Patients in both ECOG PS 0-1 and ECOG PS 2-3 responded to antioxidant treatment.
REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L55 ANSWER 24 OF 80 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2003:25084 BIOSIS
DOCUMENT NUMBER: PREV200300025084

TITLE: alpha-**Lipoic acid** inhibits LPS-induced adhesion molecule expression in mice in vivo.
AUTHOR(S): Zhang, Wei-Jian [Reprint Author]; Frei, Balz [Reprint Author]
CORPORATE SOURCE: Linus Pauling Institute, Oregon State University, Corvallis, OR, USA
SOURCE: Free Radical Biology and Medicine, (2002) Vol. 33, No. Supplement 2, pp. S347. print.
Meeting Info.: 9th Annual Meeting of the Oxygen Society. San Antonio, Texas, USA. November 20, 2002. International Society for Free Radical Research.
ISSN: 0891-5849 (ISSN print).
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 1 Jan 2003
Last Updated on STN: 1 Jan 2003

L55 ANSWER 25 OF 80 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2002:186230 BIOSIS
DOCUMENT NUMBER: PREV200200186230
TITLE: Effect of increased concentration of D-glucose or L-fucose on monocyte **adhesion** to endothelial **cell** monolayers and activation of nuclear factor-kappaB.
AUTHOR(S): Yorek, Mark A. [Reprint author]; Dunlap, Joyce A.
CORPORATE SOURCE: 3 E 17 Veterans Affairs Medical Center, Iowa City, IA, 52246, USA
SOURCE: Metabolism Clinical and Experimental, (February, 2002) Vol. 51, No. 2, pp. 225-234. print.
CODEN: METAAJ. ISSN: 0026-0495.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 6 Mar 2002
Last Updated on STN: 6 Mar 2002

AB Increased adhesion of monocytes to endothelial cells has been linked to the development and progression of atherosclerosis in humans with diabetes. Previous studies have shown that increased concentration of glucose and subsequent generation of reactive oxygen species and the activation of the transcription factor nuclear factor-kappaB (NF-kappaB) may mediate this response. However, our studies have shown that in addition to glucose, other monosaccharides, such as L-fucose, which is increased in circulation in diabetes, may also contribute to the development of diabetic complications. In these studies, we examined the effect of an increased concentration of L-fucose on monocyte adhesion to cultured bovine aorta endothelial cells. Exposing cultured bovine aorta endothelial cells to an increased concentration of either glucose or L-fucose caused a concentration-dependent increase in adhesion of monocytes. The increase in monocyte adhesion induced by glucose or L-fucose was preceded by the activation of NF-kappaB and the generation of reactive oxygen species. The combination of glucose and L-fucose at a submaximal concentration did not appear to have an additive effect on the induction of monocyte adhesion. The addition of alpha-**lipoic acid** partially prevented the glucose and L-fucose-induced activation of NF-kappaB, generation of reactive oxygen species, and increase in monocyte adhesion. This suggests that the effect of an increased concentration of glucose or L-fucose on monocyte **adhesion** to endothelial **cells** is at least partially due

to the production oxygen-derived free radicals. Furthermore, these studies provide evidence that monosaccharides other than glucose that are increased in the circulation of humans with diabetes may contribute to vascular defects in diabetes.

L55 ANSWER 26 OF 80 EMBASE
on STN

ACCESSION NUMBER: 2002171883 EMBASE
TITLE: Evaluation of selected chemopreventive agents present in common foods in mouse mammary gland organ culture.
AUTHOR: Hawthorne M.; Steele V.; Mehta R.G.
CORPORATE SOURCE: R.G. Mehta, Department of Surgical Oncology, University of Illinois, 840 S. Wood St., Chicago, IL 60612, United States. raju@uic.edu
SOURCE: Pharmaceutical Biology, (2002) 40/SUPPL. (70-74).
Refs: 25
ISSN: 1388-0209 CODEN: PHBIFC
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 016 Cancer
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Prevention of cancer by natural and synthetic non-toxic chemopreventive agents has become a major research area in the past 15 years. The naturally occurring chemopreventive agents from the herbal medicine and edible plants can be evaluated in a variety of bioassays and identified for their activity as cancer preventive agents. We have adapted a mouse mammary gland organ culture assay (MMOC) for evaluating chemically pure chemopreventive agents for their activity to inhibit 7,12-dimethylbenz(a)anthracene (DMBA)-induced mammary alveolar lesions (MAL). Here, we report a list of 32 agents that are found in the herbs or edible foods and showing inhibition of more than 55% in MMOC. From the studies reported in the literature it appears that there is a good correlation between the effects in MMOC and effects observed with in vivo carcinogenesis models. Recently, we have modified the MMOC assay to evaluate efficacy of chemopreventive agents specifically the ones that may have anti-estrogenic activity. Thus, MMOC provides a valuable tool for preliminary evaluation of chemopreventive agents prior to conducting a long-term animal carcinogenesis studies.

L55 ANSWER 27 OF 80 EMBASE
on STN

ACCESSION NUMBER: 2003370156 EMBASE
TITLE: Integrative tumor board: Esophageal cancer.
AUTHOR: De la Torre M.; Bugno T.J.; Gustin D.M.; Agarwal M.; Motwani B.; Nathan D.; Fulop J.A.; Augustine M.; Lo C.H.; Yance Jr. D.R.; Krost B.; Devi N.J.; Little S.; Block K.I.
CORPORATE SOURCE: Dr. M. De la Torre, Block Ctr. Integrative Cancer Care, 1800 Sherman Avenue, Evanston, IL 60201, United States. Mdelatorre@blockmedical.com
SOURCE: Integrative Cancer Therapies, (2002) 1/1 (44-66).
ISSN: 1534-7354 CODEN: ICTNAY
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer

032 Psychiatry
037 Drug Literature Index
039 Pharmacy
048 Gastroenterology
LANGUAGE: English

L55 ANSWER 28 OF 80 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2001:833099 HCAPLUS
DOCUMENT NUMBER: 135:362605
TITLE: Nutritional preparation comprising ribose and folic acid and medical use thereof
INVENTOR(S): Hageman, Robert Johan Joseph; Smeets, Rudolf Leonardus Lodewijk; Verlaan, George
PATENT ASSIGNEE(S): N.V. Nutricia, Neth.
SOURCE: PCT Int. Appl., 29 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001085178	A1	20011115	WO 2001-NL349	20010508
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6420342	B1	20020716	US 2000-566381	20000508
EP 1282426	A1	20030212	EP 2001-930315	20010508
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2003532679	T2	20031105	JP 2001-581831	20010508
US 2002183263	A1	20021205	US 2002-178736	20020625
US 6548483	B2	20030415		

PRIORITY APPLN. INFO.: US 2000-566381 A 20000508
WO 2001-NL349 W 20010508

AB Trauma, surgery, inflammation, subfertility, lactation problems, gut disorders, infant nutrition, cancer, arthritis and other joint problems, vascular problems and cardio- or cerebrovascular problems, ischemia, aging, impaired immune function, burns, sepsis, malnutrition, problems with liver or kidneys, malaria, cystic fibrosis, migraine, neurol. problems, respiratory infections, improvement of sports results, muscle soreness, drug intoxication and pain can be treated with a nutritional compn. contg. effective amts. of ribose and folic acid, optionally combined with other components such as niacin, histidine, glutamine, orotate, vitamin B6 and other components.
REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L55 ANSWER 29 OF 80 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2001:693317 HCAPLUS

DOCUMENT NUMBER: 135:257089
TITLE: Preparation and use of novel lipoic acid heterocyclic or benzene derivatives as medicines
INVENTOR(S): Harnett, Jeremiah; Auguet, Michel
PATENT ASSIGNEE(S): Societe de Conseils de Recherches et d'Applications Scientifiques (S.C.R.A.S.), Fr.
SOURCE: PCT Int. Appl., 49 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001068643	A2	20010920	WO 2001-FR764	20010315
WO 2001068643	A3	20020606		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
FR 2806409	A1	20010921	FR 2000-3355	20000316
FR 2806409	B1	20020419		
EP 1265891	A2	20021218	EP 2001-917143	20010315
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2003527391	T2	20030916	JP 2001-567734	20010315
US 2003105107	A1	20030605	US 2002-221432	20020910

PRIORITY APPLN. INFO.:
FR 2000-3355 A 20000316
FR 2000-12007 A 20000921
WO 2001-FR764 W 20010315

OTHER SOURCE(S): CASREACT 135:257089; MARPAT 135:257089

AB The invention concerns novel heterocyclic or benzene derivs., e.g., I [A = N:C(A')NH2; A' = linear or branched C1-6-alkyl, 5-6 membered aryl or heterocycle; B1, B2 = (CH2)n; P = (CH2)g, R6-substituted phenylene; XY = O(CH2)r, NR3(CH2)r, CO(CH2)r, CONR3(CH2)2, NR4CO(CH2)r, NR3CONR4(CH2)r; X'Y' = (CH2)r, (CH2)rO(CH2)r, (CH2)rNR3(CH2)r,(CH2)rCO(CH2)r, (CH2)rCONR3(CH2)r, (CH2)rNR4CO(CH2)r,(CH2)NR3rCONR4(CH2)r; Z1, Z2 = 5-6 membered arom. heterocyclic, 4-7 non-arom. heterocyclic; Ph, C6H5R5; R1, R2 = H, linear or branched C1-6-alkyl; R3, R4 = H, alkyl, alkoxycarbonyl, aralkoxycarbonyl; R5 = H, linear or branched C1-6-alkyl, (CH2)m-Q; Q = H, OH, CN, NH2, alkoxy, (di)alkylamino; R6 = linear or branched C1-6-alkyl, (CH2)n-Q'; Q' = halogen, CF3, OH, NH2, CN, alkoxycarbonyl, aralkoxycarbonyl, alkoxy, alkylthio, (di)alkylamino; n = 0 - 6; g = 0 - 6; r = 0 - 6; m = 0 - 6] and II, their pharmaceutically acceptable salts, comprising a lateral chain derived from lipoic acid, having an activity inhibiting NO-synthase enzymes producing NO nitrogen monoxide and/or are agents enabling regeneration of antioxidants or entities trapping reactive oxygen species (ROS) and intervening more generally in the redox status of thiol groups, methods for prepg. them, pharmaceutical compns. contg. them and their therapeutic use, particularly their use as NO-synthase inhibitors and/or as agents involved more generally in the redox status of

thiol groups. Thus, thiophenecarboximidamide III.cntdot.HCl was prepd. from DL-thioctic acid, HS(CH2)2CH(SH)(CH2)4CO2H, via amidation with N-(p-nitrophenyl)piperazine, nitro group redn. and condensation with S-methyl-2-thiophenethiocarboximide hydroiodide. III.cntdot.HCl was tested for inhibition of NO synthase from rat cerebellum (CI50 = 4.5 .mu.M) and for its effect on oxidative stress induced by glutamate on HT-22 cell cultures (CE50 = 4 .mu.M).

L55 ANSWER 30 OF 80 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2001:319711 HCAPLUS
DOCUMENT NUMBER: 134:331632
TITLE: Pharmaceutical compositions containing protein kinase C inhibitors and antioxidants
INVENTOR(S): Cameron, Norman Eugene; Ways, Douglas Kirk
PATENT ASSIGNEE(S): Eli Lilly and Co., USA
SOURCE: PCT Int. Appl., 52 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001030331	A2	20010503	WO 2000-US26254	20001013
WO 2001030331	A3	20020124		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1999-161129P P 19991022
US 2000-177510P P 20000121
OTHER SOURCE(S): MARPAT 134:331632
AB Compns. comprising a PKC inhibitor, or a salt and an antioxidant, essential fatty acid, or a prostacyclin agent, or a pharmaceutically acceptable salt thereof are provided. Also provided are methods of treatment comprising administration of such compns., and methods of treatment comprising co-administration of a PKC inhibitor, or a pharmaceutically acceptable salt thereof, and an antioxidant, essential fatty acid, or a prostacyclin agent, or a salt. Thus, an aerosol contained drug 0.35, EtOH 29.75, propellant-22 70.0%.

L55 ANSWER 31 OF 80 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2001:50483 HCAPLUS
DOCUMENT NUMBER: 134:105879
TITLE: Pharmaceutical and nutritional compositions containing essential fatty acids and homocysteine-lowering agents
INVENTOR(S): Horrobin, David Frederick; Gouaille, Christina
PATENT ASSIGNEE(S): Scarista Limited, UK
SOURCE: PCT Int. Appl., 23 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent

LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001003696	A1	20010118	WO 2000-GB2681	20000711
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
BR 2000013157	A	20020402	BR 2000-13157	20000711
EP 1200085	A1	20020502	EP 2000-948105	20000711
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
JP 2003504333	T2	20030204	JP 2001-508976	20000711
EE 200200021	A	20030415	EE 2002-21	20000711
NZ 516101	A	20030630	NZ 2000-516101	20000711
NO 2002000090	A	20020108	NO 2002-90	20020108
ZA 2002000259	A	20021022	ZA 2002-259	20020111

PRIORITY APPLN. INFO.: GB 1999-16536 A 19990714
WO 2000-GB2681 W 20000711

AB The combined application of at least one essential fatty acid of the n-6 or n-3 series, optionally together with further essential fatty acid(s) of the n-6 or n-3 series, together with one or more homocysteine-lowering agent is described. The homocysteine lowering agent is selected from vitamin B12, folic acid, a compd. related to folic acid with similar biol. activity and vitamin B6. Hard or soft gelatin capsules contained 500 mg of Et eicosapentaenoate or eicosapentaenoic acid triglyceride, together with 1 mg of hydroxocobalamin, 1 mg of folic acid and 2 mg of pyridoxine, to be taken 2-4 times a day.

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L55 ANSWER 32 OF 80 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2001:12255 HCAPLUS
DOCUMENT NUMBER: 134:66145
TITLE: A method using inositol hexaphosphate and other compounds for optimizing immune activity in the treatment of autoimmune diseases and chronic immune conditions
INVENTOR(S): Jacobs, Robert H.
PATENT ASSIGNEE(S): USA
SOURCE: PCT Int. Appl., 35 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 2001000194 A2 20010104 WO 2000-IB791 20000613
WO 2001000194 A3 20011220
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
PRIORITY APPLN. INFO.: US 1999-141437P P 19990629
US 2000-177387P P 20000124

AB A method and compn. are provided for optimizing immune activity in the treatment of chronic immune conditions wherein the chronic immune conditions is Hepatitis C. A method and compn. are described for reducing the inflammation and the viral activity in the hepatocytes in living mammals and for reducing the no. of carcinogenic free radicals, including hydroxyl and superoxide anions, in living mammals, and for enhancing the immune system in HIV/AIDS-infected individuals by enhancing the bodily mechanisms including intracellular communication, gene regulation, gene repair, and membrane effects. A method and compn. are provided for optimizing immune activity under conditions of chronic immune conditions in the treatment of such chronic immune conditions, where the chronic immune conditions include Hepatitis-C, Cancer, AIDS/HIV, herpes, colds, influenza, bronchitis, chronic fatigue and Epstein-Barr. The term chronic immune conditions is defined to include cancer, AIDS/HIV, hepatitis C, herpes, colds, influenza, bronchitis, chronic fatigue and Epstein-Barr. A method and compn. are provided for optimizing immune activity, which comprises administering to the mammal a safe and effective daily max. amt. of a mixt. of (a) inositol hexaphosphate or a physiol. acceptable salt thereof; (b) inositol or a physiol. acceptable salt thereof; (c) N-acetylcysteine; (d) .alpha.-lipoic acid;. and (e) a combination of .beta.-sitosterol and .beta.-sitosterolin, in the ratio of wt. in milligrams of (a):(b):(c):(d), (e) from about 8000 to 10,000 mg of (a), from about 80 to 250 mg of (b), from about 200 to 1500 mg of (c), from about 50 to 300 mg of (d), and from 5 to 50 mg of (e).

L55 ANSWER 33 OF 80 MEDLINE on STN DUPLICATE 1
ACCESSION NUMBER: 2001643876 MEDLINE
DOCUMENT NUMBER: 21548002 PubMed ID: 11689467
TITLE: Alpha-lipoic acid inhibits TNF-alpha-induced NF-kappaB activation and adhesion molecule expression in human aortic endothelial cells.
AUTHOR: Zhang W J; Frei B
CORPORATE SOURCE: Linus Pauling Institute, Oregon State University, Corvallis, Oregon 97331, USA.
CONTRACT NUMBER: HL-56170 (NHLBI)
HL-60886 (NHLBI)
SOURCE: FASEB JOURNAL, (2001 Nov) 15 (13) 2423-32.
Journal code: 8804484. ISSN: 1530-6860.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200112
ENTRY DATE: Entered STN: 20011107

Last Updated on STN: 20020123
Entered Medline: 20011205

AB Endothelial activation and monocyte adhesion are initiating steps in atherogenesis thought to be caused in part by oxidative stress. The metabolic thiol antioxidant alpha-lipoic acid has been suggested to be of therapeutic value in pathologies associated with redox imbalances. We investigated the role of (R)-alpha-lipoic acid (LA) vs. glutathione and ascorbic acid in tumor necrosis factor alpha (TNF-alpha) -induced adhesion molecule expression and nuclear factor kappaB (NF-kappaB) signaling in human aortic endothelial cells (HAEC). Preincubation of HAEC for 48 h with LA (0.05-1 mmol/l) dose-dependently inhibited TNF-alpha (10 U/ml) -induced adhesion of human monocytic THP-1 cells, as well as mRNA and protein expression of E-selectin, vascular **cell adhesion** molecule 1 and intercellular adhesion molecule 1. LA also strongly inhibited TNF-alpha-induced mRNA expression of monocyte chemoattractant protein-1 but did not affect expression of TNF-alpha receptor 1. Furthermore, LA dose-dependently inhibited TNF-alpha-induced IkappaB kinase activation, subsequent degradation of IkappaB, the cytoplasmic NF-kappaB inhibitor, and nuclear translocation of NF-kappaB. In contrast, TNF-alpha-induced NF-kappaB activation and adhesion molecule expression were not affected by ascorbic acid or by manipulating cellular glutathione status with l-2-oxo-4-thiazolidinecarboxylic acid, N-acetyl-l-cysteine, or d,l-buthionine-S,R-sulfoximine. Our data show that clinically relevant concentrations of LA, but neither vitamin C nor glutathione, inhibit adhesion molecule expression in HAEC and monocyte adhesion by inhibiting the IkappaB/NF-kappaB signaling pathway at the level, or upstream, of IkappaB kinase.

L55 ANSWER 34 OF 80 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 2
ACCESSION NUMBER: 2002:332144 BIOSIS
DOCUMENT NUMBER: PREV200200332144
TITLE: Antioxidant and anti-AGE therapy: Appraisal and prospects. Original Title: Therapeutiques anti-oxydantes et anti-AGE: Bilans et perspectives.
AUTHOR(S): Bonnefont-Rousselot, Dominique [Reprint author]
CORPORATE SOURCE: Laboratoire de Biochimie Metabolique et Clinique, UFR des Sciences Pharmaceutiques et Biologiques, 4, avenue de l'Observatoire, 75270, Paris Cedex, 06, France
SOURCE: Journal de la Societe de Biologie, (2001) Vol. 195, No. 4, pp. 391-398. print.
ISSN: 1295-0661.
DOCUMENT TYPE: Article
LANGUAGE: French
ENTRY DATE: Entered STN: 12 Jun 2002
Last Updated on STN: 12 Jun 2002

AB Diabetic patients exhibit an oxidative stress status, that is an imbalance between reactive oxygen species and antioxidant defences, in favour of the first ones. This oxidative stress, together with formation of advanced glycation endproducts (AGEs), is involved in diabetic complications. It could thus be of great interest to propose antioxidant and/or anti-AGE therapeutics as complementary treatment in these patients. Antioxidants can be classical molecules such as vitamin E, **lipoic acid** or N-acetylcysteine. Thus, vitamin E supplementation can improve insulin efficiency and glycemic equilibrium, as shown by the decrease of glycaemia, glycated haemoglobin and fructosamine values. In addition, this kind of supplementation lowers plasma lipid peroxidation

and oxidizability of low density lipoproteins, which is involved in the atherogenesis process. Moreover, it allows to fight against complications such as retinopathy. A second category is represented by molecules able to fight against the effects of glycation end-products (AGEs). They can act: - either by preventing cellular action of AGEs; this is obtained with soluble receptors of advanced glycation endproducts (sRAGE); - or by inhibiting AGE formation (scavenging of reactive carbonyl intermediates). Nucleophilic compounds such as pyridoxamine, tenilsetam, 2,3-diaminophenazone, OPB-9195 or aminoguanidine can act in this way. Aminoguanidine is able to limit the development of the main diabetes-associated complications in animals. A double-blind clinical assay has been conducted in type 2 diabetic patients in the United States and the Canada, in order to determine if aminoguanidine is able to slow down the progression of diabetes-induced nephropathy. We will discuss about another guanidic molecule, i.e. metformin, which is also able to scavenge AGEs, in the last part of this review. A third category of molecules is constituted by oral antidiabetic molecules exhibiting antioxidant properties. They are thiazolidinediones (troglitazone) and sulfonylureas (gliclazide). Troglitazone and gliclazide can thus decrease LDL oxidizability and monocyte **adhesion** to endothelial **cells**, which is an early step in the atherogenesis process and which is stimulated by oxidised LDLs. Finally, a prospective way is devoted to oral anti-diabetic drugs exhibiting both antioxidant and anti-AGE properties. A very used antidiabetic drug of interest is metformin (dimethylbiguanide), since it can prevent diabetes complications not only by lowering glycaemia, but also by inhibiting AGE formation and by stimulating antioxidant defences. The latter therapeutic approach constitutes a future way in the diabetes area, in order both to obtain a better glycemic control and a least development of diabetic complications.

L55 ANSWER 35 OF 80 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2001:79960 HCAPLUS
DOCUMENT NUMBER: 135:136208
TITLE: Immunotherapy (recombinant interleukin 2), hormone therapy (medroxyprogesterone acetate) and antioxidant agents as combined maintenance treatment of responders to previous chemotherapy
AUTHOR(S): Mantovani, Giovanni; Maccio, Antonio; Madeddu, Clelia; Massa, Elena; Mudu, Maria Caterina; Mulas, Carlo; Gramignano, Giulia; Massidda, Stefania; Murgia, Viviana; Lusso, Maria Rita; Mura, Loredana
CORPORATE SOURCE: Department of Medical Oncology, University of Cagliari, Cagliari, I-09124, Italy
SOURCE: International Journal of Oncology (2001), 18(2), 383-391
CODEN: IJONES; ISSN: 1019-6439
PUBLISHER: International Journal of Oncology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB An open, non-randomized phase II study was carried out including all patients treated with whatever chemotherapy or combined modality regimen for whatever cancer who were in clin. objective response or stable disease (SD) for more than three months, to receive maintenance treatment with recombinant interleukin-2 (rIL-2) plus medroxyprogesterone acetate (MPA) plus antioxidant agents alpha-lipoic acid (ALA) and N-acetyl cysteine (NAC). The main study endpoints were clin. outcome and toxicity. The secondary endpoints were effects of treatment on cancer-related

anorexia/cachexia syndrome (CACS) symptoms, on serum levels of proinflammatory cytokines, IL-2, C-reactive protein (CRP) and leptin as well as the evaluation of quality of life (QL). RIL-2 was administered at a dose of 1.8 MIU s.c. three times/wk on alternate days for the first two weeks of every month and MPA was given orally at a dose of 500 mg once a day at alternate days without interruption. ALA 300 mg/day orally and NAC 1800 mg/day orally were also administered. The treatment was administered until progression of disease or appearance of toxicity. From July 1998 to May 2000, 16 patients were enrolled in the study (M/F ratio: 15/1; mean age: 62 yr, range 45-71). The median duration of maintenance treatment was 10 mo (range 5-22). The response to maintenance treatment at Sept. 2000 was: CR (persistent throughout the treatment) 4 patients (25%); SD 1 patient (6.2%); PD 11 patients (68.8%). The median duration of response was 9.8 mo (range: 5-22+). The median follow-up duration was 19 mo (range: 8-102). The median OS was not reached. The median PFS was 14 mo (range 1-29). The 1-yr survival rate was 25%. At Sept. 2000, 9 patients are still surviving. No grade 3/4 toxicity was obsd. One Grade 2 skin toxicity was obsd. and Grade 1: 2 fever, 2 thrombocytopenia, 1 neutropenia and 1 skin were obsd. The ECOG PS did worsen significantly, the body wt. and BMI increased significantly after treatment, whereas the appetite did not change significantly. The QL evaluation showed a significant amelioration of cognitive functions and a borderline significant amelioration of emotional functions after treatment, whereas a borderline worsening of dyspnea was obsd. The abs. lymphocyte count increased significantly after the maintenance treatment, as well as the serum IL-2, TNF.alpha. decreased at borderline statistical significance; the serum levels of leptin did not change significantly. The evaluation of patient subgroups showed that responders/survivors had a pattern superimposable to that of whole patient population, the patients who rapidly progressed and died exhibited no significant changes of these parameters during treatment. The results of the present study suggest that the host immune response, evaluated by several parameters, after IL-2 administration, (e.g. lymphocytosis), are worth further study as potential markers for the major end points of cancer treatment, i.e. OS and QL, in an adequate no. of patients.

REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L55 ANSWER 36 OF 80 EMBASE
on STN

ACCESSION NUMBER: 2001338249 EMBASE
TITLE: Laminin .alpha.2 chain (merosin M chain) distribution and VEGF, FGF(2), and TGF.beta.1 gene expression in angiogenesis of supraglottic, lung, and breast carcinomas.
AUTHOR: Vitolo D.; Ciocci L.; Cicerone E.; Rossi C.; Tiboni F.; Ferrauti P.; Gallo A.; Baroni C.D.
CORPORATE SOURCE: Prof. C.D. Baroni, 2nd Chair of Pathology, Dept. Experimental Medicine/Pathol., University 'La Sapienza', Viale Regina Elena 324, 00161 Roma, Italy.
carlo.baroni@uniromal.it
SOURCE: Journal of Pathology, (2001) 195/2 (197-208).
Refs: 41
ISSN: 0022-3417 CODEN: JPTLAS
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
011 Otorhinolaryngology

015 Chest Diseases, Thoracic Surgery and Tuberculosis
016 Cancer
029 Clinical Biochemistry

LANGUAGE: English
SUMMARY LANGUAGE: English

AB The prognostic significance of vessel quantification in human solid tumours is still debated, due to the presence of multiple factors modulating neoangiogenesis and the invasiveness of neoplastic cells. This study examined ten supraglottic squamous carcinomas, ten non-small cell lung carcinomas (three squamous, five bronchioloalveolar, two adenocarcinomas), and nine classic (NOS) invasive ductal breast carcinomas. The properties studied in these tumours were vascularity; the immunohistochemical distribution of adhesion molecules such as .alpha.2.beta.1, .alpha.3.beta.1, .alpha.4.beta.1, .alpha.5.beta.1, .alpha.6.beta.4, and ICAM-1 in endothelial cells; extracellular matrix proteins (ECMPs) and laminin .alpha.2 chain (merosin M chain) in **basal membranes** of vessels; and gene expression of vascular endothelial growth factor (VEGF), basic fibroblast growth factor (FGF(2)), and transforming growth factor .beta.1 (TGF.beta.1), by in situ hybridization. Independently of tumour type and vascularity, laminin .alpha.2 chain expression was observed in the **basal membranes** of a limited proportion of vessels. In vitro experiments demonstrated laminin .alpha.2 chain expression mainly in early endothelial cell cultures, suggesting that laminin .alpha.2 chain expression in vivo can be considered a marker of early angiogenesis. Stromal and parenchymal vascularity was associated with laminin .alpha.2 chain expression in supraglottic carcinomas, whereas in the other tumours, laminin .alpha.2 chain positive vessels were observed only in the stroma. In supraglottic carcinomas, VEGF-positive cells were mainly represented by neoplastic cells, whereas in the other tumours, the great majority of VEGF-positive cells were macrophages and fibroblasts. FGF(2)- and TGF.beta.1-positive cells were macrophages and fibroblasts in all tumours. These observations suggest that in addition to the quantification and distribution of vessels, evaluation of their maturation may contribute to a better understanding of the role of angiogenesis in the growth and spread potential of solid tumours. In this regard, in supraglottic carcinomas, parenchymal angiogenesis seems to be regulated mainly by neoplastic cells, which may help to explain their high metastatic potential; in solid tumours of different histogenesis, different cells might be responsible for modulating tumour angiogenesis. Copyright .COPYRGT. 2001 John Wiley & Sons, Ltd.

L55 ANSWER 37 OF 80 HCAPLUS COPYRIGHT 2003 ACS on STN DUPLICATE 3
ACCESSION NUMBER: 2000:741922 HCAPLUS
DOCUMENT NUMBER: 133:291098
TITLE: .alpha.-Lipoic acid in prevention or treatment of tumor **metastasis**
INVENTOR(S): Colacci, Annamaria; Vaccari, Monica; Cabri, Walter; Bernasconi, Ermanno
PATENT ASSIGNEE(S): Antibioticos S.p.A., Italy
SOURCE: PCT Int. Appl., 20 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000061143	A1	20001019	WO 2000-EP3100	20000407
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
IT 99MI0728	A1	20001009	IT 1999-MI728	19990409
IT 1312060	B1	20020404		
EP 1173166	A1	20020123	EP 2000-920675	20000407
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				

PRIORITY APPLN. INFO.: IT 1999-MI728 A 19990409
WO 2000-EP3100 W 20000407

AB The invention relates to the use of .alpha.-lipoic acid, as well as its derivs. in the control of tumor progression and in the antimetastatic therapy. .alpha.-Lipoic acid induced a redn. in **cell** migration while enhancing **adhesion** to the matrix. A 500-.mu.M concn. induced a 2.5-fold increase in adhesion to laminin and to collagen IV, and 1.5-fold increase in adhesion to fibronectin and to vitronectin.

REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L55 ANSWER 38 OF 80 HCAPLUS COPYRIGHT 2003 ACS on STN DUPLICATE 4
ACCESSION NUMBER: 2000:592551 HCAPLUS
DOCUMENT NUMBER: 133:172167
TITLE: Use of lipoic acid combination with ascorbic acid in the treatment of cancer
INVENTOR(S): Casciari, Joseph; Riordan, Neil H.
PATENT ASSIGNEE(S): Center for the Improvement of Human Functioning International, Inc., USA
SOURCE: PCT Int. Appl., 14 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000048594	A1	20000824	WO 2000-US3656	20000211
W: AE, AL, AM, AT, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, CZ, DE, DE, DK, DK, DM, EE, EE, ES, FI, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6284786	B1	20010904	US 1999-249872	19990216
US 6448287	B1	20020910	US 1999-359498	19990723

EP 1152758 A1 20011114 EP 2000-907281 20000211
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO
JP 2002537253 T2 20021105 JP 2000-599386 20000211
US 2002037917 A1 20020328 US 2001-956525 20010918
PRIORITY APPLN. INFO.: US 1999-249872 A 19990216
US 1999-359498 A1 19990723
WO 2000-US3656 W 20000211

AB Lipoic acid and/or its water sol. salt is used to treat cancer, alone or in combination with ascorbic acid (vitamin C). Alone or in combination, it was shown to be effective on in vitro tumors and mouse tumors. The agents can be administered safely, and have been used effectively in case studies.

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L55 ANSWER 39 OF 80 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2000:396492 HCAPLUS
DOCUMENT NUMBER: 133:54572
TITLE: Small molecular weight ligand-hexose containing pharmacokinetic clearing agents
INVENTOR(S): Theodore, Louis J.; Axworthy, Donald B.; Reno, John M.
PATENT ASSIGNEE(S): NeoRx Corporation, USA
SOURCE: U.S., 88 pp., Cont.-in-part of U.S. Ser. No. 163,184, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 14
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6075010	A	20000613	US 1994-350551	19941207
US 5283342	A	19940201	US 1992-895588	19920609
WO 9325240	A2	19931223	WO 1993-US5406	19930607
WO 9325240	A3	19940217		
W: CA, JP, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
EP 1138334	A2	20011004	EP 2001-201994	19930607
EP 1138334	A3	20020403		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE				
US 5911969	A	19990615	US 1994-329617	19941026
US 5624896	A	19970429	US 1995-462765	19950605
US 6172045	B1	20010109	US 1996-659761	19960606
US 6416738	B1	20020709	US 2000-561736	20000425
US 2003129191	A1	20030710	US 2002-125788	20020417

PRIORITY APPLN. INFO.: US 1992-895588 B2 19920609
US 1992-995381 B2 19921223
WO 1993-US5406 A2 19930607
US 1993-163184 B2 19931207
US 1992-995383 A2 19921223
EP 1993-915235 A3 19930607
US 1994-350551 A2 19941207
US 2000-561736 A1 20000425

OTHER SOURCE(S): MARPAT 133:54572
AB Small mol. wt. clearing agents contg. ligands such as biotin or biotin

analogs and hexose residues, in particular galactose or N-acetyl galactosamine residues are taught. These clearing agents effectively clear anti-ligand contg. conjugates in vivo via hepatocyte receptor-mediated clearance mechanisms.

REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L55 ANSWER 40 OF 80 WPIX COPYRIGHT 2003 THOMSON DERWENT on STN
ACCESSION NUMBER: 2000-148701 [14] WPIX
DOC. NO. CPI: C2000-046786
TITLE: Culturing human cancer cells for molecular biology research comprises culturing fragments of tissue slices.
DERWENT CLASS: B04 D16
INVENTOR(S): JORDAN, A
PATENT ASSIGNEE(S): (JORD-I) JORDAN A; (MAGF-N) MAGFORCE APPL GMBH
COUNTRY COUNT: 25
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
DE 19912798	C1	20000217	(200014)*		10
WO 2000053728	A2	20000914	(200047)	GE	
RW: AT BE CH CY DE DK EA ES FI FR GB GR IE IT LU MC NL PT SE					
W: AU CN JP KR US					
AU 2000040986	A	20000928	(200067)		
EP 1165753	A2	20020102	(200209)	GE	
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE					
KR 2002013507	A	20020220	(200257)		
CN 1351655	A	20020529	(200258)		
JP 2002537829	W	20021112	(200275)		31

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
DE 19912798	C1	DE 1999-19912798	19990310
WO 2000053728	A2	WO 2000-DE528	20000218
AU 2000040986	A	AU 2000-40986	20000218
EP 1165753	A2	EP 2000-920340	20000218
		WO 2000-DE528	20000218
KR 2002013507	A	KR 2001-711262	20010904
CN 1351655	A	CN 2000-804737	20000218
JP 2002537829	W	JP 2000-603351	20000218
		WO 2000-DE528	20000218

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 2000040986	A	Based on	WO 2000053728
EP 1165753	A2	Based on	WO 2000053728
JP 2002537829	W	Based on	WO 2000053728

PRIORITY APPLN. INFO: DE 1999-19912798 19990310
AB DE 19912798 C UPAB: 20000320
NOVELTY - A method (I) for culturing cancer cells from human tissue for molecular biology research, is new and comprises spatially resolving a

tissue sample comprising tumor cells, normal cells and contaminants, into a series of parallel slices, dividing the slices into tissue fragments and introducing the separated tissue fragments and fluids into a cell culture medium under conditions selective for growth.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for an apparatus (II) for carrying out (I), comprising:

(a) a cutting apparatus, comprising:

(i) a collecting tray divided into compartments with subcompartments;

(ii) a cutting board removably attached to the collecting tray and provided with cutting grooves in alignment with the subcompartments; and

(iii) a cutter frame equipped with blades in alignment with the cutting grooves; and

(b) a comminution apparatus, comprising:

(i) a drip tray divided into compartments;

(ii) a preparation plate removably attached to the drip tray and provided with wells having holes aligned above the compartments; and

(iii) rotary punches aligned with the wells.

USE - The method is useful for preparing cultures of tumor cells in order to study their structure, growth and malignancy or to determine the efficacy of therapies.

ADVANTAGE - The method produces reproducible results in a relatively short time (a few days).

DESCRIPTION OF DRAWING(S) - The drawing shows (II) for cutting the sample into slices:

Collecting tray 1
Cutting board 2
Cutter frame 3
Cutting grooves 4
Sample 6
Blades. 10
Dwg.1/5

L55 ANSWER 41 OF 80 EMBASE COPYRIGHT 2003 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2001130303 EMBASE
TITLE: Ototoxicity: Mechanisms, protective agents, and monitoring.
AUTHOR: Campbell K.C.M.; Kalkanis J.; Glatz F.R.
CORPORATE SOURCE: Dr. K.C.M. Campbell, Department of Surgery, Division of Otolaryngology, SIU School of Medicine, 801 N. Rutledge Street, Springfield, IL 62794-9629, United States. kcampbell@SIUmed.edu
SOURCE: Current Opinion in Otolaryngology and Head and Neck Surgery, (2000) 8/5 (436-440).
Refs: 24
ISSN: 1068-9508 CODEN: COOSFD
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 011 Otorhinolaryngology
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
052 Toxicology
LANGUAGE: English
SUMMARY LANGUAGE: English

AB In the past year, progress has been made not only in elucidating the mechanisms of ototoxicity but also in finding otoprotective agents. For aminoglycosides, new dosing protocols and protective agents, including

growth factors and salicylates, show promise for eventually reducing ototoxicity. Further evidence of genetic susceptibility has been published. For chemotherapeutic agents, further evidence of oxidative damage and ion channel blockade mechanisms reinforces earlier work. Protective agents for cisplatin-induced ototoxicity have been further investigated including antioxidants and metal binders. Protection has been demonstrated not only for the organ of Corti but also for the stria vascularis. For audiologic monitoring of ototoxicity, new methods of collecting and interpreting high-frequency audiometry, auditory brain stem responses, and otoacoustic emissions have been proposed to enhance early detection. High-frequency audiometry has also been proposed to monitor industrial solvent exposure. .COPYRGT. 2000 Lippincott Williams & Wilkins, Inc.

L55 ANSWER 42 OF 80 MEDLINE on STN
ACCESSION NUMBER: 2000474345 MEDLINE
DOCUMENT NUMBER: 20318169 PubMed ID: 10862506
TITLE: Dose-dependent protection by lipoic acid against cisplatin-induced nephrotoxicity in rats: antioxidant defense system.
AUTHOR: Somani S M; Husain K; Whitworth C; Trammell G L; Malafa M; Rybak L P
CORPORATE SOURCE: Department of Pharmacology, Southern Illinois University School of Medicine, Springfield 62794-9629, USA.. ssomani@wpsmtp.siumed.edu
CONTRACT NUMBER: R01DC02396-02 (NIDCD)
SOURCE: PHARMACOLOGY AND TOXICOLOGY, (2000 May) 86 (5) 234-41. Journal code: 8702180. ISSN: 0901-9928.
PUB. COUNTRY: Denmark
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200010
ENTRY DATE: Entered STN: 20001012
Last Updated on STN: 20001012
Entered Medline: 20001005

AB This study was designed to investigate the role of graded doses of lipoic acid pretreatment against cisplatin-induced nephrotoxicity. Male Wistar rats were divided into six groups and treated as follows: 1) vehicle (saline) control; 2) cisplatin (16 mg/kg, intraperitoneally); 3) lipoic acid (100 mg/kg, intraperitoneally); 4) cisplatin plus lipoic acid (25 mg/kg); 5) cisplatin plus lipoic acid (50 mg/kg) and 6) cisplatin plus lipoic acid (100 mg/kg). Rats were sacrificed three days after treatment, and plasma as well as kidneys were isolated and analyzed. Plasma creatinine increased (677% of control) following cisplatin administration alone which was decreased by lipoic acid in a dose-dependent manner. Cisplatin-treated rats showed a depletion of renal glutathione (GSH), increased oxidized GSH and decreased GSH/GSH oxidized ratio (62%, 166% and 62% of control), respectively which were restored with lipoic acid pretreatment. Renal superoxide dismutase, catalase, glutathione peroxidase (GSH peroxidase) and glutathione reductase activities decreased (62%, 75%, 62% and 80% of control), respectively, and malondialdehyde content increased (204% of control) following cisplatin administration, which were restored with increasing doses of lipoic acid. The renal platinum concentration increased following cisplatin administration, which was possibly decreased by chelation with lipoic acid. The data suggest that the graded doses of lipoic acid effectively prevented a decrease in

renal antioxidant defense system and prevented an increase in lipid peroxidation, platinum content and plasma creatinine concentrations in a dose-dependent manner.

L55 ANSWER 43 OF 80 EMBASE COPYRIGHT 2003 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2000205856 EMBASE
TITLE: [Molecular mechanisms of cancer progression]. MOLEKULARGENETISCHE GRUNDLAGEN DER PROGRESSION MALIGNER ERKRANKUNGEN.
CORPORATE SOURCE: Dr. B. Wullich, Klin./Poliklin. Urol./Kinderurolog., Universitat des Saarlandes, 66421 Homburg/Saar. bernd@wullich.de
SOURCE: Urologe - Ausgabe A, (2000) 39/3 (222-227). Refs: 5 ISSN: 0340-2592 CODEN: URGABW
COUNTRY: Germany
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
LANGUAGE: German
SUMMARY LANGUAGE: English; German
AB During the past decade, the molecular mechanisms in the process of tumor progression, including **metastasis** and angiogenesis, have become better understood. Cancer **metastasis** consists of multiple, complex interacting steps. Each of these steps is crucial and limiting, since a failure to complete any one prevents the tumor cell from producing a **metastasis**. Detachment from the solid tumor by loosening the intercellular junctions and proteolysis of the extracellular matrix enables tumor cells to enter blood and lymph vessels. The intravasation into the circulation is supported by the secretion of angiogenic factors, which induce degradation of the **basal membrane** in blood vessels. **Adhesion** to endothelial **cells**, extravasation from the circulation, and induction of angiogenesis are further essential steps for completing the metastatic process. Furthermore, it is well known that once a tumor cell has entered circulation, it will survive only by evasion of the immune system. The systematic identification of tumor antigens opens up new possibilities for immunotherapeutic approaches.

L55 ANSWER 44 OF 80 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2000:442746 BIOSIS
DOCUMENT NUMBER: PREV200000442746
TITLE: Modulation by antioxidants of endothelial apoptosis, proliferation and associated gene/protein expression.
AUTHOR(S): Artwohl, M. [Reprint author]; Schmetterer, L. [Reprint author]; Rainer, G. [Reprint author]; Waldhausl, W. [Reprint author]; Baumgartner-Parzer, S. [Reprint author]
CORPORATE SOURCE: Dept. of Int. Med. III, Div. of Endocrinology and Metabolism, Univ. Vienna, Vienna, Austria
SOURCE: Diabetologia, (August, 2000) Vol. 43, No. Supplement 1, pp. A69. print.
Meeting Info.: 36th Annual Meeting of the European Association for the Study of Diabetes. Jerusalem, Israel. September 17-21, 2000. European Association for the Study of Diabetes.
CODEN: DBTGAJ. ISSN: 0012-186X.
DOCUMENT TYPE: Conference; (Meeting)

Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 18 Oct 2000
Last Updated on STN: 10 Jan 2002

L55 ANSWER 45 OF 80 HCAPLUS COPYRIGHT 2003 ACS on STN DUPLICATE 5
ACCESSION NUMBER: 1999:113547 HCAPLUS
DOCUMENT NUMBER: 130:177548
TITLE: Method of treating disease using a tocotrienol and .alpha.-lipoic acid or derivatives or an ester thereof
INVENTOR(S): Berry, Christopher J.; Foley, John L.; Packer, Lester
PATENT ASSIGNEE(S): Thailand
SOURCE: PCT Int. Appl., 41 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9906040	A1	19990211	WO 1998-US16207	19980804
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9887680	A1	19990222	AU 1998-87680	19980804

PRIORITY APPLN. INFO.: US 1997-55433P P 19970804
WO 1998-US16207 W 19980804

AB Antioxidant or combination of antioxidants are disclosed which function particularly well in modulating the action of free radicals and in particular which function particularly well in regulating activation of a transcription factor (e.g. NF-.kappa.B) and which can be non-toxically administered to a human or an animal. In particular, a method is disclosed for treating diseases, including redn. of the incidence of lung cancers in tobacco smokers, using a tocotrienol and .alpha.-lipoic acid or tocotrienyl lipoate or derivs. thereof.
REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L55 ANSWER 46 OF 80 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1999:640701 HCAPLUS
DOCUMENT NUMBER: 131:252595
TITLE: Agents and methods for modulation of zinc transfer by metallothionein
INVENTOR(S): Vallee, Bert L.; Maret, Wolfgang
PATENT ASSIGNEE(S): The Endowment for Research In Human Biology, Inc., USA
SOURCE: PCT Int. Appl., 125 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9949860	A1	19991007	WO 1999-US7432	19990329
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2326771	AA	19991007	CA 1999-2326771	19990329
AU 9934703	A1	19991018	AU 1999-34703	19990329
EP 1067922	A1	20010117	EP 1999-916366	19990329
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				

PRIORITY APPLN. INFO.:		
US 1998-79969P	P	19980330
US 1998-84953P	P	19980511
WO 1999-US7432	W	19990329

AB A method is provided for the treatment of diseases of plants and animals where such diseases involve disturbance of zinc homeostasis. The method involves administration of therapeutic agents that alter cellular oxidn. potential so as to oxidize metallothionein and thereby release zinc ions, or as to maintain metallothionein in a reduced state so as to prevent transfer of zinc from metallothionein to zinc acceptors. Modulators of zinc release from metallothioneins are oxidizing or reducing agents, such as ebselen, selenocystine, selenocysteine, selenocystamine, selenocysteamine, selenoglutathione, selenoglutathione disulfide, glutathione, glutathione disulfide, ascorbate, dehydroascorbate, etc. These agents are useful for treatment of various diseases, such as diseases of CNS, cancer, viral infections, inflammation, autoimmune diseases, etc. E.g., selenocystine at equimolar concns. with respect to the 20 thiol ligands of metallothionein affected transfer of zinc to 4-(2-pyridylazo)resorcinol as an acceptor. Zinc transfer under these conditions could not be quenched by even a 30 fold excess of glutathione indicating some specificity of selenocystine towards metallothionein in comparison to glutathione. Addnl., substoichiometric amts. of selenocystine (50 nM compared to 10 .mu.M thiols) enhanced zinc transfer in the presence of an addnl. oxidant (butylhydroperoxide), indicating that this biol. selenium compd. acts catalytically on the reaction of metallothionein with a peroxide resulting in zinc release.

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L55 ANSWER 47 OF 80 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1999:640546 HCAPLUS

DOCUMENT NUMBER: 131:252560

TITLE: 6,8-dimethylmercaptooctanoic acid derivatives substituted at 6-S and/or 8-S by a 3-methylthiopropanoyl radical, their preparation, and pharmaceutical compositions containing them for the treatment of cancer

INVENTOR(S): Quash, Gerard Anthony; Gore, Jacques; Fournet, Guy

PATENT ASSIGNEE(S): Galderma Research and Development, S.N.C., Fr.

SOURCE: Eur. Pat. Appl., 26 pp.

CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 947503	A1	19991006	EP 1999-400803	19990401
EP 947503	B1	20011121		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
FR 2777001	A1	19991008	FR 1998-4041	19980401
FR 2777001	B1	20000609		
US 6117902	A	20000912	US 1999-281654	19990330
AU 9922536	A1	19991014	AU 1999-22536	19990331
AU 747867	B2	20020523		
JP 2000001471	A2	20000107	JP 1999-95560	19990401
JP 3459884	B2	20031027		
AT 209184	E	20011215	AT 1999-400803	19990401
ES 2167989	T3	20020516	ES 1999-400803	19990401

PRIORITY APPLN. INFO.: FR 1998-4041 A 19980401
OTHER SOURCE(S): MARPAT 131:252560
AB Derivs. of 6,8-dimethylmercaptooctanoic acid substituted at 6-S and/or 8-S with a 3-methylthiopropanoyl radical (Markush included) are prepd. for the treatment of cancer. Compds. of the invention include e.g. Me 6-mercapto-8-S-(3-methylthiopropanoyl)octanoate.
REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L55 ANSWER 48 OF 80 WPIX COPYRIGHT 2003 THOMSON DERWENT on STN
ACCESSION NUMBER: 2000-087222 [07] WPIX
CROSS REFERENCE: 1998-286959 [25]
DOC. NO. CPI: C2000-024353
TITLE: Enhancing transient expression of foreign DNA in eukaryotic cells by treatment with e.g. carboxylic or sulfonic acid derivatives, useful in gene therapy or recombinant protein production.
DERWENT CLASS: B04 D16
INVENTOR(S): GOFFE, A S; GOFFE, R A
PATENT ASSIGNEE(S): (GENE-N) GENESPAN CORP
COUNTRY COUNT: 87
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9964578	A1	19991216	(200007)*	EN	82
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ UG ZW					
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZA ZW					
AU 9944254	A	19991230	(200022)		
EP 1084237	A1	20010321	(200117)	EN	
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE					
CN 1306569	A	20010801	(200172)		

JP 2002517235 W 20020618 (200242) 99

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 9964578	A1	WO 1999-US12752	19990607
AU 9944254	A	AU 1999-44254	19990607
EP 1084237	A1	EP 1999-927318	19990607
		WO 1999-US12752	19990607
CN 1306569	A	CN 1999-807164	19990607
JP 2002517235	W	WO 1999-US12752	19990607
		JP 2000-553568	19990607

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 9944254	A	Based on	WO 9964578
EP 1084237	A1	Based on	WO 9964578
JP 2002517235	W	Based on	WO 9964578

PRIORITY APPLN. INFO: US 1998-93449 19980608

AB WO 9964578 A UPAB: 20020704

NOVELTY - Enhancing transient expression of a foreign gene in eukaryotic cells comprising introducing foreign DNA into the cell, treating the cell with a transient expression-enhancing agent (I) (before, during or after transformation), maintaining the cell on a non-selective medium and after at least 4 days detecting the foreign protein (II) in the cells, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(a) identifying (I) comprises:

(i) treating two batches ((1) and (2)) of SW480 P3 cells (day 0) with expressible foreign DNA;

(ii) before, during or after introduction of DNA, treating batch 2 with a test compound; and

(iii) cumulatively measuring the amount of foreign protein expressed in both batches between days 0 and 4, 4 and 7 or 4 and 14, and using these amounts to determine X, G7 and G14 for the respective time periods, calculated as 100-(100A)/C (where A and C are the amounts of protein produced in untreated and treated cells, respectively and values of X, G7 or G14 over 10, particularly over 25, indicate an active (I))

(b) manipulating the metabolism of a cell to reduce consumption of glucose by treating with an agent (I') that induces the use of proteins and amino acids as a primary energy source; and

(c) increasing **adhesion** of a **cell** to a culture substrate by adding a sulfonated aminopolysaccharide (SAP) to the culture medium.

ACTIVITY - Anticancer; anorectic.

MECHANISM OF ACTION - Gene therapy; vaccine.

USE - (I) are used to increase transient gene expression in vivo, e.g. in conjunction with naked DNA vaccines, or other gene therapy methods such as expression of interleukin-2 for cancer treatment, to test efficacy of new antitumor agents, recombinant protein production in body fluids and cells. (I) may also induce a switch from glucose to protein (and possibly lipids) as the main energy source (potentially useful for treating obesity), endogenous phosphatase activity (allowing transgene expression

to be monitored) or an increase in **cell adhesion** and **cell**-to-**cell** contact, (particularly to allow growth of hepatocytes without a feeder layer).

ADVANTAGE - The method increases the efficiency, amount and duration of transgene expression, without requiring selection or integration of DNA into the host cell genome.

Dwg.0/5

L55 ANSWER 49 OF 80 EMBASE on STN

ACCESSION NUMBER: 2000298789 EMBASE

TITLE: Laminin receptors in differentiated thyroid tumors: Restricted expression of the 67-kilodalton laminin receptor in follicular carcinoma cells.

AUTHOR: Montuori N.; Muller F.; De Riu S.; Fenzi G.; Sobel M.E.; Rossi G.; Vitale M.

CORPORATE SOURCE: Dr. N. Montuori, Dipto. Biol./Patol. Cell./Molecolare, via S. Pansini 5, 80131 Naples, Italy. mavitale@cds.unina.it

SOURCE: Journal of Clinical Endocrinology and Metabolism, (1999) 84/6 (2086-2092).
Refs: 39
ISSN: 0021-972X CODEN: JCEMAZ

COUNTRY: United States

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 003 Endocrinology
016 Cancer

LANGUAGE: English

SUMMARY LANGUAGE: English

AB The expression of integrin laminin receptors was investigated in normal thyroid primary cultures; immortalized normal thyroid cells (TAD-2); papillary (NPA), follicular (WRO), and anaplastic (ARO) thyroid tumor cell lines; seven thyroid tumors (four papillary and three follicular carcinomas); and normal thyroid glands. The expression of .alpha.1.beta.1, .alpha.2.beta.1, .alpha.3.beta.1, .alpha.6.beta.1, .alpha.6.beta.4 was found in all tumor specimens and in tumor cell lines, whereas normal thyroid cells and TAD-2 cells lacked the expression of .alpha.6.beta.4. Despite the presence of several integrin laminin receptors, adhesion of TAD-2, NPA, and ARO cells to immobilized laminin-1 was poor, whereas WRO cells and follicular carcinoma-derived **cells** displayed a strong **adhesion**. Indeed, WRO and follicular carcinoma-derived cells showed expression of a nonintegrin laminin receptor, the 67-kDa high affinity laminin receptor (67LR). TAD-2, NPA, and ARO cells as well as nodular goiter, toxic adenoma, follicular adenoma, and papillary carcinoma-derived cells did not express the 67LR. Adhesion of WRO and follicular carcinoma-derived cells to laminin-1 was specifically inhibited by a recombinant polypeptide containing laminin-binding domains of 67LR, demonstrating that this receptor confers to follicular carcinoma cells attachment capacity to laminin. Moreover, tissue specimens from follicular carcinomas expressed the 67LR, whereas follicular adenomas and normal thyroid tissues were negative. In thyroid tumors, integrin receptors, although abundant, participate weakly in adhesion to laminin. The expression in follicular carcinoma cells of a functional, high affinity 67LR together with nonfunctional integrin LM receptors could be responsible for the tendency of follicular carcinoma cells to **metastasize** by mediating stable contacts with **basal membranes**.

L55 ANSWER 50 OF 80 MEDLINE on STN
ACCESSION NUMBER: 2000031961 MEDLINE
DOCUMENT NUMBER: 20031961 PubMed ID: 10562616
TITLE: Systemic hypoxia promotes leukocyte-endothelial adherence via reactive oxidant generation.
AUTHOR: Wood J G; Johnson J S; Mattioli L F; Gonzalez N C
CORPORATE SOURCE: Department of Molecular and Integrative Physiology, University of Kansas Medical Center, Kansas City, Kansas 66160, USA.
CONTRACT NUMBER: ES/HL-09293 (NIEHS)
HL39443 (NHLBI)
SOURCE: JOURNAL OF APPLIED PHYSIOLOGY, (1999 Nov) 87 (5) 1734-40. Journal code: 8502536. ISSN: 8750-7587.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199912
ENTRY DATE: Entered STN: 20000113
Last Updated on STN: 20000113
Entered Medline: 19991222

AB We recently demonstrated that systemic hypoxia during reduced inspired PO(2) produces a rapid increase in leukocyte adherence to rat mesenteric venules. Evidence suggests that the mechanism of this response involves decreased nitric oxide (NO) levels. One possible pathway for NO depletion could involve increased reactive oxygen species (ROS) generation resulting in inactivation of NO. The overall goal of the present study was to examine the role of ROS in promoting leukocyte-endothelial adherence during systemic hypoxia. Experiments were designed to 1) evaluate changes in ROS generation in the mesenteric microcirculation during systemic hypoxia, 2) determine how the ROS signal changes when PO(2) levels return to normal after a period of systemic hypoxia, 3) assess the effect of antioxidants on ROS generation during hypoxia, and 4) utilize antioxidants to examine the functional relationship between ROS generation and leukocyte adherence during hypoxia. The major findings from this study are that systemic hypoxia increases ROS generation within the mesenteric microcirculation and that antioxidants prevent the increase in leukocyte-endothelial adhesive interactions observed in hypoxia.

L55 ANSWER 51 OF 80 DRUGU COPYRIGHT 2003 THOMSON DERWENT on STN
ACCESSION NUMBER: 2000-28856 DRUGU P
TITLE: Alpha-**lipoic acid** inhibits TNF-alpha induced expression of adhesion molecules in human aortic endothelial cells.
AUTHOR: Zhang W; Rocha A; Hagen T; Frei B
CORPORATE SOURCE: Linus-Pauling-Inst.
LOCATION: Corvalis, Oreg., USA
SOURCE: Circulation (100, No. 18, Suppl., 813, 1999)
CODEN: CIRCAZ ISSN: 0009-7322
AVAIL. OF DOC.: Linus Pauling Institute, Corvallis, Oregon, U.S.A.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature

AB This study investigated the effect of lipoate-alpha (LA) on the TNF-alpha induced expression of adhesion molecules in cultured human aortic endothelial cells. LA (0, 0.5, 0.1, 0.2, 0.5 and 1.0 mM)

dose-dependently decreased TNF-alpha-induced protein expression of E-selectin and vascular-**cell adhesion** molecule-1 (VCAM-1), with 64% and 71% inhibition respectively at a concentration of 0.5 mM. LA had no effect on the expression of intracellular adhesion molecule-1, but it increased the intracellular levels of GSH by 61% and the thiol redox status by 11-fold. Therefore LA at clinical concentrations decreased E-selectin and VCAM-1 expression which may suggest a therapeutic role in the prevention and treatment of atherosclerosis and inflammation. (conference abstract: 72nd Scientific Sessions of the American Heart Association, Atlanta, Georgia, USA, 1999). (No EX).

L55 ANSWER 52 OF 80 EMBASE COPYRIGHT 2003 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 1999050901 EMBASE
TITLE: Integrin .alpha.6.beta.1 role in metastatic behavior of human pancreatic carcinoma cells.
AUTHOR: Vogelmann R.; Kreuser E.D.; Adler G.; Lutz M.P.
CORPORATE SOURCE: M.P. Lutz, Department of Internal Medicine I, University of Ulm, 89081 Ulm, Germany. manfred.lutz@medizin.uni-ulm.de
SOURCE: International Journal of Cancer, (1999) 80/5 (791-795). Refs: 21
ISSN: 0020-7136 CODEN: IJCNAW
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
048 Gastroenterology
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The factors that determine the metastatic behavior of pancreatic tumor cells are incompletely understood. In this study, we first demonstrate differences in adhesion properties, integrin expression and in vivo integrin function in the metastatic tumor cell line PaTu 8988s compared with the non- metastatic cell line PaTu 8988t. Both cell lines were derived from the same original tumor and exhibit identical genetic fingerprints. Using in vitro adhesion assays performed on purified extracellular matrix components, **adhesion** of PaTu 8988s **cells** was significantly increased on the **basal membrane** component laminin and decreased on the interstitial matrix protein fibronectin compared to PaTu 8988t cells. By immunocytochemistry and flow cytometry, and in correspondence with their adhesive properties, the metastatic PaTu 8988s cells did express a distinct pattern of integrin subunits. Laminin-binding integrins .alpha.6 and .beta.4 were overexpressed in PaTu 8988s cells. Fibronectin-binding .alpha.5 integrins were present at higher levels in the non-metastatic PaTu 8988t cells, whereas the .beta.1 subunit expression did not differ. Adhesion to laminin or fibronectin was specific and was mediated via integrins .alpha.6.beta.1 and .alpha.5.beta.1, respectively. In addition, **metastasis** formation in vivo after injection of cells into the tail vein of nude mice was inhibited by preincubation of PaTu 8988s cells with antibodies directed against the integrin .alpha.6 or .beta.1. We conclude that .alpha..beta.1 integrins are overexpressed and functionally active in metastatic human pancreatic carcinoma cells, and participate in **metastasis** formation probably through binding to the **basal membrane** component laminin.

L55 ANSWER 53 OF 80 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1999:710732 HCAPLUS
DOCUMENT NUMBER: 132:189360
TITLE: Combined effect of lipoic acid and doxorubicin in murine leukemia
AUTHOR(S): Dovinova, I.; Novotny, L.; Rauko, P.; Kvasnicka, P.
CORPORATE SOURCE: Cancer Research Institute, Slovak Academy of Sciences, Bratislava, 833 91, Slovakia
SOURCE: Neoplasma (1999), 46(4), 237-241
CODEN: NEOLA4; ISSN: 0028-2685
PUBLISHER: Slovak Academic Press Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Our expts. indicate that administration of a toxic drug with high rate of free-radical formation (doxorubicin, DOX) combined with an antioxidant (.alpha.-lipoic acid, LA) may lead to a decrease in drug-toxicity. However, the effects of antioxidant may be concn.-dependent and it is therefore crucial to choose its appropriate dosage. LA at a low concn. (1 .mu.mol/l) acts as a growth factor and at a higher concn. (100 .mu.mol/l) acts as an antiproliferation agent. Both concns. of LA in combination with DOX were examd. in cytotoxic and antitumor effects in L1210 mouse leukemia cells employing a MTT chemosensitivity assay. In most concn. combinations, DOX and LA effect were antagonistic and synergistic action was only found at the higher concn. of both agents (DOX 2.5 .mu.mol/l and LA 100 .mu.mol/l). Use of LA in doxorubicin therapy lead to an increase (though marginally significant) in survival of animals. Combined single-dose administration of DOX (5 mg/kg) and LA (16 mg/kg) lead to super-additive effect of the combination on survival of leukemic mice.

REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L55 ANSWER 54 OF 80 MEDLINE on STN
ACCESSION NUMBER: 1999237206 MEDLINE
DOCUMENT NUMBER: 99237206 PubMed ID: 10220857
TITLE: Dose dependent protection by lipoic acid against cisplatin-induced ototoxicity in rats: antioxidant defense system.
AUTHOR: Rybak L P; Husain K; Whitworth C; Somani S M
CORPORATE SOURCE: Department of Pharmacology, Southern Illinois University, School of Medicine, Springfield 62794, USA.
CONTRACT NUMBER: R01DC0239602 (NIDCD)
SOURCE: TOXICOLOGICAL SCIENCES, (1999 Feb) 47 (2) 195-202.
Journal code: 9805461. ISSN: 1096-6080.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199907
ENTRY DATE: Entered STN: 19990715
Last Updated on STN: 19990715
Entered Medline: 19990707

AB This study investigated the alterations that occur in auditory brainstem-evoked responses (ABRs) concurrent with changes in cochlear concentrations of glutathione (GSH), lipid peroxidation, and antioxidant enzyme activity in cisplatin-induced ototoxicity and in dose-dependent otoprotection by an antioxidant lipoate. Male Wistar rats were divided into different groups and were treated as follows, with: (1) vehicle (saline) control; (2) cisplatin (16 mg/kg, i.p.); (3) lipoate (100 mg/kg,

i.p.) plus saline; (4) cisplatin plus lipoate (25 mg/kg); (5) cisplatin plus lipoate (50 mg/kg), and (6) cisplatin plus lipoate (100 mg/kg). Post-treatment ABRs were evaluated after three days, the rats were sacrificed, and cochleae were harvested and analyzed. The cisplatin-injected rats showed ABR threshold elevations above the pre-treatment thresholds. Rats treated with lipoate plus cisplatin did not show significant elevation of hearing thresholds. Cisplatin administration resulted in a depletion of cochlear GSH concentration (69% of control), whereas, cisplatin-plus-lipoate treatment increased GSH concentration close to control value. Cisplatin-treated rats showed a decrease in cochlear superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GSH-Px), and glutathione reductase (GR) activities (57, 78, 59, and 58% of control, respectively), and an increase in malondialdehyde (MDA) concentration (196% of control). Cochlear SOD, CAT, GSH-Px, and GR activities and MDA concentrations were restored in the rats injected with cisplatin plus graded doses of lipoate than those with cisplatin alone. It is concluded that cisplatin-induced ototoxicity is related to impairment of the cochlear antioxidant defense system, and the dose-dependent otoprotection conferred by an antioxidant lipoate against cisplatin ototoxicity is associated with sparing of the cochlear antioxidant defense system.

L55 ANSWER 55 OF 80 MEDLINE on STN
ACCESSION NUMBER: 2000301408 MEDLINE
DOCUMENT NUMBER: 20301408 PubMed ID: 10842591
TITLE: Ototoxicity. Amelioration by protective agents.
AUTHOR: Rybak L P; Somani S
CORPORATE SOURCE: Department of Surgery, Southern Illinois University, School of Medicine, Springfield 62794-9638, USA.
CONTRACT NUMBER: RO1-DC 002396 (NIDCD)
SOURCE: ANNALS OF THE NEW YORK ACADEMY OF SCIENCES, (1999 Nov 28) 884 143-51.
Journal code: 7506858. ISSN: 0077-8923.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200006
ENTRY DATE: Entered STN: 20000706
Last Updated on STN: 20000706
Entered Medline: 20000627

AB The findings of studies from this laboratory are summarized to compare the efficacy of four chemoprotective agents against the effects of cisplatin-induced hearing loss and biochemical damage in the rat cochlea. A number of studies have shown that cisplatin is ototoxic, resulting in hearing loss, morphologic damage, and biochemical changes in the cochlea. These studies used Wistar rats, which underwent pre- and posttreatment ABR testing using clicks and tonebursts stimuli at 8, 16, and 32 kHz. Controls received i.p. saline injection. Cisplatin-treated rats were given 16 mg/kg cisplatin i.p. Animals received protective agents in the following dosage: DDTC protected rats received 600 mg/kg subcutaneously an hour after cisplatin. MTBA-protected animals were given 250 mg/kg i.p. 30 minutes before cisplatin. Animals protected with ebselen received 16 mg/kg i.p. an hour before cisplatin. One hundred mg/kg of alpha-lipoic acid was injected i.p. 30 minutes before cisplatin. Rats were sacrificed three days after treatment and the cochleae were harvested and frozen in liquid nitrogen and stored at -80 degrees C until analysis of glutathione

(GSH), the activity of antioxidant enzymes (superoxide dismutase, catalase, glutathione peroxidase, and glutathione reductase) and malondialdehyde was performed. Cisplatin-treated rats were found to have ABR threshold shifts of 27-40 dB, and rats treated with chemoprotective agents plus cisplatin all had ABR thresholds shifts of less than 10 dB. Significant depletion of glutathione and decrease of the activities of the antioxidant enzymes were observed in cisplatin-treated rats. These changes were accompanied by a marked elevation of malondialdehyde. These changes were almost completely prevented by the use of the chemoprotective agents. These findings suggest that cisplatin ototoxicity is related to lipid peroxidation and that the use of protective agents prevents hearing loss and lipid peroxidation by sparing the antioxidant defense system in the cochlea.

L55 ANSWER 56 OF 80 EMBASE
on STN

ACCESSION NUMBER: 1999115837 EMBASE
TITLE: Polarographic properties and potential carcinogenicity of some natural nucleosides and their synthetic analogues.
AUTHOR: Novotny L.; Vachalkova A.; Piskala A.
CORPORATE SOURCE: L. Novotny, Department Pharmaceutical Chemistry, Faculty of Pharmacy, Kuwait University, POB 5969, 13060 Safat, Kuwait
SOURCE: Bioelectrochemistry and Bioenergetics, (1999) 48/1 (129-134).
Refs: 18
ISSN: 0302-4598 CODEN: BEBEBP
PUBLISHER IDENT.: S 0302-4598(99)00005-7
COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
027 Biophysics, Bioengineering and Medical Instrumentation
030 Pharmacology
037 Drug Literature Index
052 Toxicology
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The polarographic reduction and the index of potential carcinogenicity tg .alpha. determined polarographically in aprotic conditions and in the presence of .alpha.-lipoic acid of nine naturally occurring and synthetic pyrimidine and six synthetic 1,3,5-triazine (5-aza) nucleosides was compared to the reduction of eight synthetic 1,3,6-triazine (6-aza) nucleosides. Nucleosides are of interest because of their key role in the nucleic acid structure and because of the antimetabolite and cytotoxic/antileukemia properties of their synthetic analogues. It was shown that polarographic reduction of the studied compounds is achieved at gradually increased potentials in the order of 6-aza<5-aza<pyrimidine nucleosides. On other hand, the potential carcinogenicity of studied compounds increases usually in the order of pyrimidine<6-aza << 5-aza nucleoside. The only compounds with remarkable potential carcinogenicity identified at this study were those ones from the 5-aza (1,3,5-triazine) antimetabolite series - arabinosyl-5-azacytosine (0.275), 5-aza-cytidine (0.295) and 5-aza-uracil (0.400) - and 2,2'-anhydrouridine (0.260). The relation of the data obtained to biological activity of nucleosides included in the study is discussed. Copyright (C) 1999 Elsevier Science S.A.

L55 ANSWER 57 OF 80 MEDLINE on STN
ACCESSION NUMBER: 2001225527 MEDLINE
DOCUMENT NUMBER: 21117375 PubMed ID: 11225735
TITLE: High expression of human 15-lipoxygenase induces NF-kappaB-mediated expression of vascular **cell adhesion** molecule 1, intercellular adhesion molecule 1, and T-**cell adhesion** on human endothelial **cells**.
AUTHOR: Viita H; Sen C K; Roy S; Siljamaki T; Nikkari T; Yla-Herttuala S
CORPORATE SOURCE: A.I. Virtanen Institute, University of Kuopio, Finland.
SOURCE: ANTIOXIDANTS & REDOX SIGNALLING, (1999 Spring) 1 (1) 83-96. Journal code: 100888899. ISSN: 1523-0864.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200104
ENTRY DATE: Entered STN: 20010502
Last Updated on STN: 20010502
Entered Medline: 20010426

AB Expression of 15-lipoxygenase (15-LO) is induced over 100-fold in early fatty streak lesions. 15-LO activity leads to the production of specific lipid hydroperoxides, which can have major effects on the expression of proinflammatory genes involved in atherogenesis. We have used retrovirus-mediated gene transfer to achieve stable high expression of 15-LO in human endothelial ECV304 cells. These cells were used to study the effects of 15-LO on the expression of vascular **cell adhesion** molecule 1 (VCAM-1) and intercellular adhesion molecule 1 (ICAM-1), activation of nuclear factor kappa B (NF-kappaB), and T-**cell adhesion** on endothelial **cells**. NF-kappaB activation was greatly potentiated by increased 15-LO activity in the stably transduced cells, and both VCAM-1 and ICAM-1 were significantly induced in these cells in response to tumor necrosis factor-alpha (TNF-alpha) and phorbol 12-myristate 13-acetate (PMA) stimulation, as studied by flow cytometry. The induction of ICAM-1 was sensitive to antioxidants in a dose-dependent manner. The adherence of Jurkat T cells on the 15-LO-expressing endothelial cells was markedly induced after PMA stimulation. These results indicate that 15-LO activity may be involved in the early pathogenesis of atherosclerosis by inducing VCAM-1 and ICAM-1 expression and by increasing T-**cell adhesion** on the endothelium.

L55 ANSWER 58 OF 80 EMBASE COPYRIGHT 2003 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 1999207620 EMBASE
TITLE: Cellular localization of CD44 correlates with cell proliferation and liver **metastasis** in colon cancer.
AUTHOR: Kondo A.; Usuki H.; Mori S.; Maeba T.; Maeta H.
CORPORATE SOURCE: A. Kondo, First Department of Surgery, Faculty of Medicine, Kagawa Medical University, 1750-1 Ikenobe, Miki-cho, Kita, Kagawa 761-073, Japan. surgery1@kms.ac.jp
SOURCE: International Journal of Clinical Oncology, (1999) 4/2 (78-83).
Refs: 29
ISSN: 1341-9625 CODEN: IJCOF6

COUNTRY: Japan
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
016 Cancer
048 Gastroenterology
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Background. The functional heterogeneity of the **cell adhesion** molecule family CD44 is explained by differences in its activity, which is regulated by alterations in the distribution of its cellular localization. The aim of the current study was to evaluate the functional differences in cancer cells according to variations in the cellular localization of CD44. Methods. Paraffin-embedded tissue sections of 34 colon cancers (obtained from 17 patients with liver **metastasis** and 17 without liver **metastasis**) were investigated. These tumors were classified according to the predominant pattern of cellular localization of CD44 (the isoforms CD44H, CD44v6, and CD44v9. For each CD44 isoform, the functional differences were investigated for a correlation between localization patterns and Ki-67 labeling index (to indicate cell proliferative activity), and for a correlation between localization patterns and liver **metastasis**. Results. On staining for CD44H, tumors displayed three localization patterns. One pattern, in which CD44H was expressed on the basal or basolateral side of the plasma membrane in cancer cells, showed a higher Ki-67 labeling index than other localization patterns ($P < 0.01$), and a higher rate of the basolateral localization pattern was observed in patients with liver **metastasis** than in those without ($P = 0.02$). On staining for CD44v6 and CD44v9, tumors showed four and three localization patterns, respectively. No significant differences in localization patterns were found in analyses of the Ki-67 labeling index and liver **metastasis** for either CD44v6 or CD44v9. Conclusions. A functional correlate of CD44H localization patterns was detected. In particular, cancer cells in which CD44H was localized at the **basal** or basolateral **membranes** were closely associated with high proliferative activity and high liver metastatic potential.

L55 ANSWER 59 OF 80 MEDLINE on STN DUPLICATE 6
ACCESSION NUMBER: 1999075888 MEDLINE
DOCUMENT NUMBER: 99075888 PubMed ID: 9857109
TITLE: Alpha-lipoic acid reduces expression of vascular **cell adhesion** molecule-1 and endothelial adhesion of human monocytes after stimulation with advanced glycation end products.
AUTHOR: Kunt T; Forst T; Wilhelm A; Tritschler H; Pfuetzner A; Harzer O; Engelbach M; Zschaebitz A; Stofft E; Beyer J
CORPORATE SOURCE: Department of Endocrinology, Langenbeckstr. 1, University of Mainz, 55131 Mainz, Germany.
SOURCE: CLINICAL SCIENCE, (1999 Jan) 96 (1) 75-82.
Journal code: 7905731. ISSN: 0143-5221.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199904
ENTRY DATE: Entered STN: 19990426
Last Updated on STN: 19990426
Entered Medline: 19990415

AB Advanced glycation end products (AGEs) have been identified as relevant mediators of late diabetic complications such as atherosclerotic disease. The endothelial migration of monocytes is one of the first steps in atherogenesis and monocyte-endothelial interaction itself is linked to the expression of **adhesion** molecules like vascular **cell adhesion** molecule-1 (VCAM-1). Recently, stimulation of VCAM-1 by AGEs has been demonstrated. Since endothelial stimulation by AGEs is followed by generation of oxygen free radicals with subsequent activation of nuclear transcription factor kappaB, we investigated the influence of alpha-lipoic acid on the expression of VCAM-1 and monocyte adherence to endothelial cells in vitro by means of cell-associated chemiluminescence assays and quantitative reverse transcriptase polymerase chain reaction using a constructed recombinant RNA standard. We found that alpha-lipoic acid was able to decrease the number of VCAM-1 transcripts from 41. 0+/-11.2 to 9.5+/-4.7 RNA copies per cell in AGE-stimulated cell cultures. Furthermore, expression of VCAM-1 was suppressed in a time- and dose-dependent manner by alpha-lipoic acid as shown by chemiluminescence endothelial cell assay. Pretreatment of endothelial cells with 0.5 mM or 5 mM alpha-lipoic acid reduced AGE-induced endothelial binding of monocytes from 22.5+/-2.9% to 18. 3+/-1.9% and 13.8+/-1.8% respectively. Thus, we suggest that extracellularly administered alpha-lipoic acid reduces AGE-albumin-induced endothelial expression of VCAM-1 and monocyte binding to endothelium in vitro. These in vitro results may contribute to the understanding of a potential antioxidative treatment of atherosclerosis.

L55 ANSWER 60 OF 80 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2000:86938 BIOSIS
DOCUMENT NUMBER: PREV200000086938
TITLE: Effect of antioxidants on TNFa-induced adhesion molecule expression in human endothelial cells.
AUTHOR(S): Zhang, Weijian [Reprint author]; Frei, Balz [Reprint author]
CORPORATE SOURCE: Linus Pauling Institute, Oregon State University, 571 Weniger Hall, Corvallis, OR, 97331, USA
SOURCE: Free Radical Biology and Medicine, (1999) Vol. 27, No. SUPPL. 1, pp. S46. print.
Meeting Info.: 6th Annual Meeting of the Oxygen Society. New Orleans, Louisiana, USA. November 18-22, 1999. The Oxygen Society.
CODEN: FRBMEH. ISSN: 0891-5849.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 1 Mar 2000
Last Updated on STN: 3 Jan 2002

L55 ANSWER 61 OF 80 DRUGU COPYRIGHT 2003 THOMSON DERWENT on STN
ACCESSION NUMBER: 1999-06461 DRUGU P
TITLE: Transcription Factor NF-kappaB. Central mediator in the immune system and inflammatory events.
AUTHOR: Ruengler P; Lyss G; Merfort I
CORPORATE SOURCE: Univ.Freiburg
LOCATION: Freiburg, Ger.
SOURCE: Pharm.Ztg. (144, No. 2, 10-18, 1999) 5 Fig. 4 Tab. 91 Ref.
CODEN: PHZIAP ISSN: 0031-7136
AVAIL. OF DOC.: Institut fur Pharmazeutische Biologie, Albert-Ludwigs-

Universitaet Freiburg, Schaenzlestrasse 1, 79104 Freiburg, Germany. (I.M.).
LANGUAGE: German
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB Mechanisms of immune system responses are reviewed with reference to the role of transcription factor NF-kappaB as a mediator, external inducers of NF-kappaB (bacteria, viruses and their products, xenobiotics and other agencies including ionizing radiation and ozone), and internal inducers of NF-kappaB (growth factors, ligands for immunoreceptors, mediators, modified proteins, **cell adhesion** and stress reactions). The regulation of NF-kappaB by phosphorylation, hydrogen peroxide and drugs including NSAIDs and corticosteroids is also discussed.

L55 ANSWER 62 OF 80 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2000:37256 BIOSIS
DOCUMENT NUMBER: PREV200000037256
TITLE: alpha-**Lipoic acid** inhibits TNFalpha-induced expression of adhesion molecules in human aortic endothelial cells.
AUTHOR(S): Zhang, Weijian [Reprint author]; Rocha, Alma [Reprint author]; Hagen, Tory [Reprint author]; Frei, Balz [Reprint author]
CORPORATE SOURCE: Linus Pauling Inst, Corvallis, OR, USA
SOURCE: Circulation, (Nov. 2, 1999) Vol. 100, No. 18 SUPPL., pp. I.813. print.
Meeting Info.: 72nd Scientific Sessions of the American Heart Association. Atlanta, Georgia, USA. November 7-10, 1999.
CODEN: CIRCAZ. ISSN: 0009-7322.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 19 Jan 2000
Last Updated on STN: 31 Dec 2001

L55 ANSWER 63 OF 80 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1998:682105 HCAPLUS
DOCUMENT NUMBER: 129:298408
TITLE: Nitrosylation to inactivate apoptotic enzymes, and therapeutic caspase-like peptide
INVENTOR(S): Lipton, Stuart A.; Troy, Carol M.
PATENT ASSIGNEE(S): The Children's Medical Center Corp., USA
SOURCE: PCT Int. Appl., 20 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9843621	A1	19981008	WO 1998-US6287	19980331

W: CA, JP
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE

EP 979073 A1 20000216 EP 1998-913316 19980331
R: DE, ES, FR, GB, IT
JP 2001518096 T2 20011009 JP 1998-541915 19980331
US 2002106404 A1 20020808 US 2002-55417 20020122
PRIORITY APPLN. INFO.: US 1997-42144P P 19970331
US 1998-52826 B1 19980331
WO 1998-US6287 W 19980331
OTHER SOURCE(S): MARPAT 129:298408
AB S-nitrosylation (reaction of nitric oxide [NO] species with crit. cysteine sulfhydryl groups of a caspase [RS] to form RS-NO) inhibits caspase activity and thereby ameliorates apoptosis not only in neuronal cells, but also in other tissues. Addnl., ICE-like (caspase-like) sequence ICARG is used to protect from excitotoxic neuronal damage and neurol. as well as non-neurol. and non-ophthalmol. indications characterized by undesired apoptosis.
REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L55 ANSWER 64 OF 80 WPIX COPYRIGHT 2003 THOMSON DERWENT on STN
ACCESSION NUMBER: 1998-508459 [44] WPIX
CROSS REFERENCE: 2001-149451 [16]
DOC. NO. CPI: C1998-153491
TITLE: Substituted dithiolane derivatives - are glutathione reductase activity enhancers useful e.g. for treating cataracts.
DERWENT CLASS: B03
INVENTOR(S): TAKASHI, F; TOMIHISA, Y; FUJITA, T; YOKOYAMA, T; TOKOYAMA, T
PATENT ASSIGNEE(S): (SANY) SANKYO CO LTD
COUNTRY COUNT: 39
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
EP 869126	A1	19981007	(199844)*	EN	416
R: AL AT BE CH DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI					
CZ 9800967	A3	19981014	(199847)		
NO 9801469	A	19981005	(199849)		
AU 9859702	A	19981008	(199901)		
ZA 9802766	A	19981230	(199907)		512
NZ 330092	A	19990429	(199923)		
CN 1208035	A	19990217	(199926)		
CA 2233682	A	19981002	(199928)		
JP 11269170	A	19991005	(199953)		214
KR 98081044	A	19981125	(200005)		
US 6013663	A	20000111	(200010)		
MX 9802679	A1	19981201	(200024)		
HU 9800743	A2	20000528	(200035)		
AU 728488	B	20010111	(200108)		
AU 2000066691	A	20010322	(200122)#		
RU 2165932	C2	20010427	(200136)		
RU 2169731	C2	20010627	(200145)		
US 6313164	B1	20011106	(200170)		
EP 869126	B1	20020731	(200257)	EN	
R: AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE					
DE 69806831	E	20020905	(200266)		

ES 2179427	T3	20030116 (200316)
BR 9806413	A	20030415 (200334)
TW 508354	A	20021101 (200352)
MX 209869	B	20020823 (200367)

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
EP 869126	A1		EP 1998-302532	19980401
CZ 9800967	A3		CZ 1998-967	19980330
NO 9801469	A		NO 1998-1469	19980401
AU 9859702	A		AU 1998-59702	19980330
ZA 9802766	A		ZA 1998-2766	19980401
NZ 330092	A		NZ 1998-330092	19980331
CN 1208035	A		CN 1998-102916	19980402
CA 2233682	A		CA 1998-2233682	19980401
JP 11269170	A		JP 1998-89033	19980401
KR 98081044	A		KR 1998-11699	19980402
US 6013663	A		US 1998-52095	19980331
MX 9802679	A1		MX 1998-2679	19980402
HU 9800743	A2		HU 1998-743	19980401
AU 728488	B		AU 1998-59702	19980330
AU 2000066691	A	Div ex	AU 1998-59702	19980330
			AU 2000-66691	20001024
RU 2165932	C2		RU 1998-106623	19980401
RU 2169731	C2		RU 1999-119545	19980401
US 6313164	B1	Div ex	US 1998-52095	19980331
			US 1999-354006	19990715
EP 869126	B1		EP 1998-302532	19980401
		Related to	EP 2000-122586	19980401
DE 69806831	E		DE 1998-606831	19980401
			EP 1998-302532	19980401
ES 2179427	T3		EP 1998-302532	19980401
BR 9806413	A		BR 1998-6413	19980402
TW 508354	A		TW 1998-104965	19980402
MX 209869	B		MX 1998-2679	19980402

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 728488	B	Previous Publ.	AU 9859702
AU 2000066691	A	Div ex	AU 728488
US 6313164	B1	Div ex	US 6013663
EP 869126	B1	Related to	EP 1070710
DE 69806831	E	Based on	EP 869126
ES 2179427	T3	Based on	EP 869126

PRIORITY APPLN. INFO: JP 1998-8837 19980120; JP 1997-83749 19970402; AU 2000-66691 20001024

AB EP 869126 A UPAB: 20031017

Dithiolane derivatives of formula (I) and their salts are new.

One of m and n = 0; the other = 0-2; k = 0-12; R1 = H, X1 or a 1-12C alkyl which is optionally interrupted by an O and/or S atom and is optionally substituted by 1-3 X1 and/or X3; A = a bond, O, CO, NR2CO, NR2CS, NR2SO2, CONR2-NR3-CO, CO-NR2-CO, CO-NR2-CS, CO-NR2-SO2, OCO,

ON(R2)CO, ON(R2)SO2, O-CON(R2)-N(R3)-CO, O-CO-N(R2)CO, OCO-N(R2)-SO2, COO, CO-CO, CO-CON(R2)-N(R3)-CO, CO-CO-N(R2)-CO, CO-CON(R2)SO2, N(R2)O, N(R2)-CO-CO, N(R2)-N(R3)CO, N(R2)-N(R3)SO2, N(R2)CON(R3)-N(R4)-CO, N(R2)-CON(R3)-CO, N(R2)CON(R3)SO2 or N(R2)-CON(R3)-SO2-N(R4)CO; R2-R4 = H, 1-12C alkyl, aralkyl (in which the aryl part is optionally substituted by 1-3 X2), acyl or X1; B = a bond, NR5 or NR6-NR5; R5, R6 = as for R2-R4; or NR1R5 = a 5-7 membered heterocycle; or where A = NR2CO, NR2CS, CONR2-NR3-CO, CO-NR2-CO, CO-NR2-CS, OCO, ON(R2)CO, O-CON(R2)-N(R3)-CO, O-CO-N(R2)CO, CO-CON(R2)-N(R3)-CO, CO-CO-N(R2)-CO, N(R2)-N(R3)CO, N(R2)CON(R3)-N(R4)-CO or N(R2)-CON(R3)-CO and B = a bond, R1 may also be OR7; or where A = CO-NR2-SO2, ON(R2)SO2, OCO-N(R2)-SO2, CO-CO, CO-CON(R2)SO2, N(R2)-CO-CO, N(R2)-N(R3)SO2, or N(R2)CON(R3)SO2 and B = a single bond; or where A is not O, COO or NR6-O and B = NR5, R1 may also be OH or OR7; R7 = lower alkyl; lower alkenyl or aralkyl (in which the aryl part is optionally substituted by 1-3 X2 or 1 X1); X1 = aryl or heterocyclyl (both optionally substituted by 1-3 X2); X2 = lower alkyl (optionally substituted by halo or OH), lower alkoxy, lower alkylthio, OH, COOH, optionally N-substituted CONH2, lower alkoxycarbonyl, halo, NO2, amino, sulpho, sulphamoyl or CN; X3 = lower alkoxy, lower alkylthio, OH, nitrooxy, COOH, lower alkoxycarbonyl, halo, sulpho, sulphamoyl, amino or optionally N-substituted CONH2; provided that: where A = O, B = a bond or NR5, where A = COO or NR2-O, B = a bond, and k = 4, -A-B-R1 is not COOH.

'aryl' = 6-14C mono or polycyclic group or is such a group fused to 3-10C cycloalkyl; 'heterocyclyl' = optionally unsaturated (preferably aromatic) 5-7 ring membered group containing 1-3 N,O and/or S; 'aralkyl' = 1-6C alkyl substituted with aryl as above; 'lower alkyl' = 1-6C; 'lower alkenyl' = 2-6C; 'amino' = NRaRb; Ra, Rb = H, lower alkyl, 3-8C cycloalkyl, aralkyl or heterocyclyl; or NRaRb = heterocyclyl; 'acyl' = an aliphatic, aromatic, or heterocyclic acyl.

USE - Claimed use is the prevention and treatment of cataracts.

The compounds may be used to treat conditions associated with oxidative stress. Such conditions include damage caused by alcohol abuse, exposure to xenobiotic agents or radiation;intracellular oxidative states caused by hepatic disease; intoxication caused by e.g. carcinostats (including Pt chelates), antibiotics, antiparasitics, paraquat, CCl4, halothane and heavy metals; nervous system disorders including degenerative disorders e.g. cerebral ischaemia, hypoglycaemia, epileptic attacks, Alzheimer's disease and Parkinson's disease; disease relating to altered immune functionality especially tumour immunotherapy; infertility (especially male); coronary heart disease; other ophthalmological disorders including retinopathy and siderosis; pulmonary conditions such as idiopathic pulmonary fibrosis, ARDS, emphysema, asthma, dysplasia and interstitial fibrosis; renal failure; gastric ulcer and **metastases** of cancer (including colorectal); diabetes; hepatocyte necrosis and apoptosis; viral disease including influenza, hepatitis B and HIV.

They may also be used to treat blood abnormalities such as Fanconi's anaemia, septicaemia, enhanced blood vessel permeability and leukocyte adherence; malformations such as Down's syndrome and favism; and inflammatory diseases such as nephritis, pancreatitis, fatigue and rheumatism.

The compounds may be administered by most conventional routes including orally, parenterally and topically, especially to the eyes including drops, ointments and solid inserts.

For an adult, oral dosage is 0.1-10000 (preferably 1-5000) mg/day; intravenously, 0.01-5000 (0.1-2000) mg/day; and topically (eyes) 0.001-500 (0.01-200) mg/day.

ADVANTAGE - The compounds are less stimulating to the eyes than

lipoic acid and other similar compounds and are especially suitable for topical application.
Dwg.0/0

L55 ANSWER 65 OF 80 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1998:206292 HCAPLUS
DOCUMENT NUMBER: 128:278644
TITLE: Inhibition of drug-naive and -resistant leukemia cell proliferation by low molecular weight thiols
AUTHOR(S): Jeitner, Thomas M.; Delikatny, Edward J.; Bartier, Wendy A.; Capper, Hugh R.; Hunt, Nicholas H.
CORPORATE SOURCE: DEPARTMENT OF PATHOLOGY, UNIVERSITY OF SYDNEY, NEW SOUTH WALES, 2006, Australia
SOURCE: Biochemical Pharmacology (1998), 55(6), 793-802
CODEN: BCPCA6; ISSN: 0006-2952
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The aim of these studies was to investigate the ability of cysteamine and its congeners to arrest the proliferation of leukemic cells and to det. the physico-chem. properties responsible for this ability. Fifteen low mol. wt. thiol-bearing compds. were shown to arrest the proliferation of CCRF-CEM cells and a methotrexate-resistant subline, with IC50 values between 10-5 and 10-4 M. Cysteamine arrested proliferation by slowing the passage of cells through S phase. These cells subsequently resumed cycling, although a proportion went on to die by apoptosis. The antiproliferative action of cysteamine was shown to depend, in part, on H2O2 prodn. This ability to generate peroxide is shared by many thiol compds., and mol. modeling indicated that thiol groups were required for the antiproliferative actions of the congeners of cysteamine. Mol. modeling also revealed that the most efficacious antiproliferative agents were those that had their amino acid and thiol moieties sepd. by an intramol. distance of 3.17 to 5.9 .ANG., as exemplified by WR 1065 and the aminothiophenols. These findings indicate that thiol-bearing compds. may have some efficacy in the treatment of drug-naive and -resistant leukemia cells.
REFERENCE COUNT: 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L55 ANSWER 66 OF 80 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1998:396337 HCAPLUS
DOCUMENT NUMBER: 129:170050
TITLE: Screening of potential cancer preventing chemicals as antioxidants in an in vitro assay
AUTHOR(S): White, E. Lucile; Ross, Larry J.; Steele, Vemon E.; Kelloff, Gary J.; Hill, Donald L.
CORPORATE SOURCE: Southern Research Institute, Birmingham, AL, 35205, USA
SOURCE: Anticancer Research (1998), 18(2A), 769-773
CODEN: ANTRD4; ISSN: 0250-7005
PUBLISHER: Anticancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
AB We used an azo-initiated fluorescence assay to rank a series of antioxidants, with the objective of selecting compds. for further evaluation as chemopreventive agents. Trolox was the pos. control for the assay and, with an IC50 of 0.50 .mu.M, was more active than any of the

other 16 compds. examd. Three compds., U83836E, glutathione, and purpurogallin, were only slightly less active with IC50's in the 1-3 .mu.M range. Four other compds. were almost as active: protocatechuic acid, N-acetyl-L-cysteine, U74389G, and lipoic acid (reduced). This fluorescence-based assay for antioxidant activity is a rapid, economical way of ranking antioxidants for further development in the National Cancer Institute's chemoprevention program.

REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L55 ANSWER 67 OF 80 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1998:547539 HCAPLUS
DOCUMENT NUMBER: 129:298031
TITLE: Cytotoxicity of lipoic acid and dihydrolipoic acid against malignant murine leukemia cells: a comparison with ascorbic acid and dehydroascorbic acid
AUTHOR(S): Roomi, M. W.; House, D.; Tsao, C. S.
CORPORATE SOURCE: Linus Pauling Institute of Science and Medicine, Palo Alto, CA, 94306, USA
SOURCE: Medical Science Research (1998), 26(7), 461-463
CODEN: MSCREJ; ISSN: 0269-8951
PUBLISHER: Lippincott-Raven Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Lipoic acid (LA) is an endogenous thiol which is reduced to dihydrolipoic acid (DHLA) in vivo. Both LA and DHLA act as antioxidants as do ascorbic acid (AA) and its oxidative product, dehydroascorbic acid (DHAA). It has been postulated that LA and DHLA interact directly with peroxy radicals in the cellular membrane and can recycle tocopheroxyl radicals back into tocopherol by a cascade mechanism involving the redn. of ascorbate. AA and DHAA have also been shown to have antitumor activity. However, very little is known about the cytotoxicity of DHLA and LA. In the present study, we compared the antitumor activity of DHLA and LA on the growth of murine leukemia P388D1 cell line to AA and DHAA. DHLA was very lethal to the fast growing malignant cells even at a low concn. with ED50 0.4 .mu.g/mL. In contrast, LA, AA and DHAA were non-toxic at lower concns., but toxicity increased with increasing concns. LA has an ED50 of 6.0 .mu.g/mL whereas both AA and DHAA have an ED50 of 3.5 .mu.g/mL. These results suggest that DHLA is considerably more cytotoxic than AA and DHAA.

REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L55 ANSWER 68 OF 80 MEDLINE on STN DUPLICATE 7
ACCESSION NUMBER: 1998330075 MEDLINE
DOCUMENT NUMBER: 98330075 PubMed ID: 9667501
TITLE: Antioxidant regulation of phorbol ester-induced adhesion of human Jurkat T-cells to endothelial cells.
AUTHOR: Roy S; Sen C K; Kobuchi H; Packer L
CORPORATE SOURCE: Department of Molecular and Cell Biology, University of California, Berkeley 94720-3200, USA..
sashwati@socrates.berkeley.edu
CONTRACT NUMBER: DK 50430 (NIDDK)
SOURCE: FREE RADICAL BIOLOGY AND MEDICINE, (1998 Jul 15) 25 (2) 229-41.
Journal code: 8709159. ISSN: 0891-5849.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199904
ENTRY DATE: Entered STN: 19990517
Last Updated on STN: 19990517
Entered Medline: 19990430

AB Regulation of adhesion molecule expression and function by reactive oxygen species via specific redox sensitive mechanisms have been reported. The effects of clinically safe antioxidants in the regulation of adhesion molecule expression in human endothelial cells (ECV), and adherence of human Jurkat T cells to ECV cells were investigated. The thiol antioxidant, alpha-lipoate, at clinically relevant doses down-regulated phorbol 12-myristate 13-acetate (PMA)-induced **adhesion** molecule expression and **cell-cell adhesion**. Inhibition of PMA-induced ICAM-1 and VCAM-1 expression as well as PMA-induced **adhesion** of Jurkat T-**cells** to ECV cells by alpha-lipoate was dose dependent (50-250 microM). The effect was significant for ICAM-1 ($p < .01$) and VCAM-1 ($p < .01$) expression in cells pretreated with 100 microM alpha-lipoate compared to PMA-activated untreated cells. Inhibition of PMA-induced **adhesion** molecule expression and **cell-cell adhesion** was more pronounced when a combination of antioxidants, alpha-lipoate and alpha-tocopherol, were used compared to the use of either of these antioxidant alone. The regulation of adhesion molecule expression and function by low concentration of antioxidants investigated does not appear to be NF-kappaB regulated or transcription dependent because no change in the mRNA response was observed. Protein kinase C (PKC) has been suggested to regulate PMA-induced adhesion molecule expression by post-transcriptional stabilization of adhesion molecule mRNA. Alpha-lipoate pretreatment did not influence the response of PKC activity to PMA. Oxidants are known to be involved in the regulation of **cell adhesion** processes. Treatment of ECV cells with PMA induced generation of intracellular oxidants. Alpha-lipoate (100 or 250 microM) treatment decreased PMA-induced generation of intracellular oxidants. The inhibitory effect of low concentration of alpha-lipaote alone or in combination with alpha-tocopherol on agonist-induced adhesion processes observed in this study may be of potential therapeutic value.

L55 ANSWER 69 OF 80 EMBASE COPYRIGHT 2003 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 96182389 EMBASE
DOCUMENT NUMBER: 1996182389
TITLE: Expression of adhesion molecules and extracellular matrix proteins in glioblastomas: Relation to angiogenesis and spread.
AUTHOR: Vitolo D.; Paradiso P.; Uccini S.; Ruco L.P.; Baroni C.D.
CORPORATE SOURCE: II Cattedra di Anatomia Patologica, Dipto Med. Sperimentale/Patologia, Viale Regina Elena 324,00161 Rome, Italy
SOURCE: Histopathology, (1996) 28/6 (521-528). ISSN: 0309-0167 CODEN: HISTDD
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
008 Neurology and Neurosurgery
016 Cancer
LANGUAGE: English

SUMMARY LANGUAGE: English

AB We studied the immunohistochemical expression of inducible adhesion molecules, integrins and extracellular matrix proteins in 10 cases of glioblastoma multiforme in order to investigate their angiogenesis, local invasiveness, poor **metastasizing** properties and their lack of tumour infiltrating leukocytes. In glioblastomas endothelial proliferations represent the majority of vascular structures; they were positive for endothelial markers (vWF, CD31, VE-cadherin) and negative for macrophage markers (CD68, PAM-1). Immunohistologically, they were subtyped into: 1 solid-glomeruloid ICAM-1, .alpha.2.beta.1, .alpha.3.beta.1, .alpha.5.beta.1 negative; 2 channelled-branching ICAM-1 negative and .alpha.2.beta.1, .alpha.3.beta.1, .alpha.5.beta.1 positive; 3 channelled-telangiectatic ICAM-1, .alpha.2.beta.1, .alpha.3.beta.1, .alpha.5.beta.1 positive. In channelled proliferations, the expression and distribution of tenascin and merosin in the **basal membrane** was similar to that of normal brain vessels. The expression of all these molecules might indicate different steps of maturation of endothelial proliferations. The majority of endothelial proliferations may be immunohistologically considered as incomplete vascular structures; this might account for the low **metastasizing** tendency and low recruitment of leukocytes by these tumours. Neoplastic astrocytes were GFAP-1, ICAM-1, VCAM-1, .alpha.2.beta.1, .alpha.3.beta.1 and .alpha.5.beta.1 immunoreactive and .alpha.6.beta.4 negative; this allows them to interact with extracellular matrix proteins and might, in part, explain the tendency of glioblastomas to infiltrate locally.

L55 ANSWER 70 OF 80 MEDLINE on STN

ACCESSION NUMBER: 96311708 MEDLINE

DOCUMENT NUMBER: 96311708 PubMed ID: 8742941

TITLE: Design, synthesis, and pharmacokinetic evaluation of a chemical delivery system for drug targeting to lung tissue.

AUTHOR: Saah M; Wu W M; Eberst K; Marvanyos E; Bodor N

CORPORATE SOURCE: Center for Drug Discovery, University of Florida College of Pharmacy, Gainesville 32610, USA.

SOURCE: JOURNAL OF PHARMACEUTICAL SCIENCES, (1996 May) 85 (5) 496-504.
Journal code: 2985195R. ISSN: 0022-3549.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199610

ENTRY DATE: Entered STN: 19961015
Last Updated on STN: 19961015
Entered Medline: 19961002

AB We espouse the application of a novel chemical delivery system (CDS) approach to a delivery mechanism for drug targeting to lung tissue using the 1,2-dithiolane-3-pentyl moiety of lipoic acid as the "targetor moiety". The synthesis and the physicochemical and pharmacokinetic evaluation of a CDS modeling the lipoyl and other ester derivatives of chlorambucil (an antineoplastic agent) and cromolyn (a bischromone used in antiasthma prophylaxis) as compared with their respective parent drugs are described. The chlorambucil CDS was synthesized by esterifying the alcohol derivative of lipoic acid with chlorambucil using dicyclohexylcarbodiimide as the coupling agent. The cromolyn CDS was prepared by a multistep synthetic procedure culminating in the reaction of the alkyl bromide derivative of lipoic acid with the disodium salt of the

bischromone compound. All the esters were highly lipophilic unlike the parent compounds. The in-vitro kinetic and in-vivo pharmacokinetic studies showed that the respective CDSs were sufficiently stable in buffer and biological media, hydrolyzed rapidly into the respective active parent drugs, and significantly enhanced delivery and retention of the active compound to lung tissue in comparison with the underivatized parent compounds used in conventional therapy.

L55 ANSWER 71 OF 80 MEDLINE on STN DUPLICATE 8
ACCESSION NUMBER: 97103878 MEDLINE
DOCUMENT NUMBER: 97103878 PubMed ID: 9011310
TITLE: [alpha-Lipoic acid--a natural disulfide cofactor and antioxidant with anticarcinogenic effects]. Kyselina alpha-lipoova--prirodny disulfidovy kofaktor a antioxidant s antikarcinogennymi ucinkami.
AUTHOR: Dovinova I
CORPORATE SOURCE: Ustav experimentalnej onkologie SAV, Bratislava.
SOURCE: CESKA A SLOVENSKA FARMACIE, (1996 Sep) 45 (5) 237-41. Ref: 49
Journal code: 9433765. ISSN: 1210-7816.
PUB. COUNTRY: Czech Republic
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: Slovak
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199702
ENTRY DATE: Entered STN: 19970219
Last Updated on STN: 19970219
Entered Medline: 19970206
AB The present survey summarizes the data about the structure, function and methods of investigation of the natural substance alpha-lipoic acid. This compound is an important growth factor of many microorganisms and at the same time a disulfide cofactor of dehydrogenases in oxidative phosphorylation. It is a physiological constituent of biological membranes, an efficient antioxidant and a scavenger of free radicals. Lipoic acid possesses anticarcinogenic and preventive effects which protect the calls from damage.

L55 ANSWER 72 OF 80 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1995:761715 HCAPLUS
DOCUMENT NUMBER: 123:152885
TITLE: New vitamin B6 derivatives and their uses in pharmaceuticals and cosmetics.
INVENTOR(S): Weischer, Carl Heinrich
PATENT ASSIGNEE(S): Germany
SOURCE: Ger. Offen., 14 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 4344751	A1	19950629	DE 1993-4344751	19931228

PRIORITY APPLN. INFO.: DE 1993-4344751 19931228

OTHER SOURCE(S): MARPAT 123:152885

AB Esters of pyridoxine, pyridoxal, pyridoxamine or their 5'-phosphates with S-contg. carboxylic acids (e.g., cysteine or its derivs.) are useful for pharmaceuticals and cosmetics. These compds. have antitumor activities, and can be used for the treatment of intestinal and skin diseases. Thus, 1-400 mg of these esters can be used in oral, parenteral, topical and inhalation dosage forms.

L55 ANSWER 73 OF 80 WPIX COPYRIGHT 2003 THOMSON DERWENT on STN
ACCESSION NUMBER: 1995-206769 [27] WPIX
DOC. NO. CPI: C1995-095801
TITLE: New complexes of palladium and **lipoic acid** - useful in treatment of psoriasis and tumours.
DERWENT CLASS: B02
INVENTOR(S): GARNETT, M
PATENT ASSIGNEE(S): (GARN-I) GARNETT M
COUNTRY COUNT: 58
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9514466	A1	19950601	(199527)*	EN	96
RW: AT BE CH DE DK ES FR GB GR IE IT KE LU MC MW NL OA PT SD SE SZ					
W: AM AT AU BB BG BR BY CA CH CN CZ DE DK ES FI GB GE HU JP KE KG KP KR KZ LK LT LU LV MD MG MN MW NL NO NZ PL PT RO RU SD SE SI SK TJ TT UA UZ VN					
AU 9511807	A	19950613	(199539)		
US 5463093	A	19951031	(199549)		48
EP 730449	A1	19960911	(199641)	EN	
R: CH DE FR GB IT LI					
US 5679697	A	19971021	(199748)		48
US 5776973	A	19980707	(199834)		
EP 730449	B1	20030402	(200325)	EN	
R: CH DE FR GB IT LI					
DE 69432429	E	20030508	(200338)		

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
WO 9514466	A1		WO 1994-US13260	19941117
AU 9511807	A		AU 1995-11807	19941117
US 5463093	A		US 1993-157570	19931126
EP 730449	A1		WO 1994-US13260	19941117
			EP 1995-902588	19941117
US 5679697	A	Div ex	US 1993-157570	19931126
			US 1995-544459	19951018
US 5776973	A	Div ex	US 1993-157570	19931126
			US 1995-544458	19951018
EP 730449	B1		WO 1994-US13260	19941117
			EP 1995-902588	19941117
DE 69432429	E		DE 1994-632429	19941117
			WO 1994-US13260	19941117
			EP 1995-902588	19941117

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 9511807	A	Based on	WO 9514466
EP 730449	A1	Based on	WO 9514466
US 5679697	A	Div ex	US 5463093
US 5776973	A	Div ex	US 5463093
EP 730449	B1	Based on	WO 9514466
DE 69432429	E	Based on	EP 730449
		Based on	WO 9514466

PRIORITY APPLN. INFO: US 1993-157570 19931126; US 1995-544459 19951018; US 1995-544458 19951018

AB WO 9514466 A UPAB: 19950712
The following are claimed: (A) complexes of (a) palladium (or a salt of this), and (b) **lipoic acid** (or a deriv. of this). (B) activated forms of vitamin B12 comprising acetyl-cystein and cyanocobalamin which have been heated together in water at pH 6.5.
USE - The new complexes act as polynucleotide reductases and are useful in treatment of tumours (e.g., carcinomas and adenocarcinomas of the lung, breast, colon, oesophagus or pancreas, malignant melanomas, liver **metastases**, or AIDS-related lymphomas or sarcomas) or psoriasis. Admin. is esp. topical or parenteral.
Dwg.0/13

L55 ANSWER 74 OF 80 MEDLINE on STN
ACCESSION NUMBER: 96050441 MEDLINE
DOCUMENT NUMBER: 96050441 PubMed ID: 8519970
TITLE: Molecular mechanisms determining the strength of receptor-mediated intermembrane adhesion.
AUTHOR: Leckband D; Muller W; Schmitt F J; Ringsdorf H
CORPORATE SOURCE: Institut fur Organische Chemie, Johannes Gutenberg Universitat, Mainz, Germany.
CONTRACT NUMBER: GM47334 (NIGMS)
SOURCE: BIOPHYSICAL JOURNAL, (1995 Sep) 69 (3) 1162-9.
Journal code: 0370626. ISSN: 0006-3495.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199601
ENTRY DATE: Entered STN: 19960219
Last Updated on STN: 19980206
Entered Medline: 19960122

AB The strength of receptor-mediated **cell adhesion** is directly controlled by the mechanism of cohesive failure between the cell surface and underlying substrate. Unbinding can occur either at the locus of the specific bond or within the bilayer, which results in tearing the hydrophobic anchors from the membrane interior. In this work, the surface force apparatus has been used to investigate the relationship between the receptor-ligand bond affinities and the dominant mechanism of receptor-coupled membrane detachment. The receptors and ligands used in this study were membrane-bound streptavidin and biotin analogs, respectively, with solution affinities ranging over 10 orders of magnitude. With the optical technique of the surface force apparatus, the occurrence of membrane rupture was directly visualized in situ. The latter observations together with measurements of the corresponding

intermembrane adhesive strengths were used to identify the dominant failure pathway for each streptavidin-analog pair. Even in cases where the membrane pull-out energy exceeded the equilibrium bond energy, cohesive failure occurred within the membrane interior at nearly all bond affinities considered. These results are consistent with previous findings and provide direct support for the commonly held view that, under nonequilibrium conditions of applied external stress, the gradient of the bond energy, not the equilibrium bond energy alone, determines the adhesive strength.(ABSTRACT TRUNCATED AT 250 WORDS)

L55 ANSWER 75 OF 80 EMBASE COPYRIGHT 2003 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 95369851 EMBASE
DOCUMENT NUMBER: 1995369851
TITLE: Inhibition of tumor cell haptotaxis by sodium D-glucaro-.delta.-lactam (ND2001).
AUTHOR: Tsuruoka T.; Azetaka M.; Iizuka Y.; Saito K.; Inouye S.; Hosokawa M.; Kobayashi H.
CORPORATE SOURCE: Medical Research Department, Pharmaceutical Division, Meiji Seika Kaisha Ltd., 4-16 Kyobashi 2-chome,Chuo-ku, Tokyo 104, Japan
SOURCE: Japanese Journal of Cancer Research, (1995) 86/11 (1080-1085).
ISSN: 0910-5050 CODEN: JJCREP
COUNTRY: Japan
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB We used the Boyden chamber system to investigate the mechanism by which the antimetastatic agent sodium D-glucaro-.delta.-lactam (ND2001) inhibits tumor cell invasion, and by establishing what ND2001 did not achieve, we were able to pinpoint the areas in which it was successful as an inhibitor. ND2001 did not inhibit **cell adhesion** of a highly metastatic B16 melanoma variant (the B16 variant) to the reconstituted **basal membrane** Matrigel, nor did it affect the production or activity of **basal membrane** -degrading type IV collagenase, but, in the Boyden chamber, ND2001 inhibited cell migration of the B16 variant toward a chemoattractant, laminin, on the lower surface of a Matrigel-free filter set (haptotaxis). Lewis lung carcinoma (3LL) cells that had been treated with ND2001 also exhibited hardly any haptotaxis, although the cells showed no alteration in behavior during **cell adhesion** to Matrigel. Since ND2001 did succeed in inhibiting the pulmonary **metastases** of the B16 variant and 3LL, we infer that inhibition of the **metastases** by ND2001 in these tumors is likely to be due to the inhibition of haptotactic migration.

L55 ANSWER 76 OF 80 EMBASE COPYRIGHT 2003 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 95194974 EMBASE
DOCUMENT NUMBER: 1995194974
TITLE: Altered expression and function of E-cadherin in cervical intraepithelial neoplasia and invasive squamous cell carcinoma.
AUTHOR: Vessey C.J.; Wilding J.; Folarin N.; Hirano S.; Takeichi

M.; Soutter P.; Stamp G.W.H.; Pignatelli M.
CORPORATE SOURCE: Department of Histopathology, Royal Postgraduate Medical School, Du Cane Road,London W12 0NN, United Kingdom
SOURCE: Journal of Pathology, (1995) 176/2 (151-159).
ISSN: 0022-3417 CODEN: JPTLAS
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
010 Obstetrics and Gynecology
016 Cancer
LANGUAGE: English
SUMMARY LANGUAGE: English
AB HECD-1 monoclonal antibody has been used to localize E-cadherin, a calcium-dependent **cell-cell adhesion** molecule, in microwave-treated, paraffin-embedded sections from 53 cases of cervical intraepithelial neoplasia (CIN) (11 CIN I, 22 CIN II, and 20 CIN III), 16 invasive cervical squamous cell carcinomas, and seven **metastases**. In normal cervix, E-cadherin was expressed on the cell **membrane** of **basal** and parabasal cells. Cytoplasmic staining was present in occasional basal cells only. In CIN, the presence and localization of cytoplasmic E-cadherin were found to be significantly correlated with the grade of the CIN lesion. In squamous cell carcinomas, reduced membranous and increased cytoplasmic staining was seen with worsening differentiation. Loss of membranous E-cadherin expression was also detected in 4/7 metastatic deposits. E-cadherin expression (120 kD form, on Western blotting) was seen in human cervical carcinoma cell lines (HT3, ME180, C4I, Caski) that maintained the ability to aggregate in a homotypic adhesion assay and showed a typical epithelial morphology. E-cadherin-negative cell lines (Hela, SiHa, C33A) did not show adhesion. HOG-1 was the only E-cadherin-negative cell line which showed a significant degree of cell-tell aggregation. These data indicate that loss of membranous E-cadherin expression may represent one of the abnormalities underlying loss of cell polarity and differentiation which characterize CIN and invasive cervical cancer.

L55 ANSWER 77 OF 80 EMBASE
on STN
ACCESSION NUMBER: 95000512 EMBASE
DOCUMENT NUMBER: 1995000512
TITLE: A novel function for the nm23-H1 gene: Overexpression in human breast carcinoma cells leads to the formation of basement membrane and growth arrest.
AUTHOR: Howlett A.R.; Petersen O.W.; Steeg P.S.; Bissell M.J.
CORPORATE SOURCE: Lawrence Berkeley Laboratory, Division of Life Sciences, University of California, 1 Cyclotron Rd.,Berkeley, CA 94720, United States
SOURCE: Journal of the National Cancer Institute, (1994) 86/24 (1838-1844).
ISSN: 0027-8874 CODEN: JNCIAM
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
016 Cancer
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Background: We have developed a culture system using reconstituted

basement membrane components in which normal human mammary epithelial cells exhibit several aspects of the development and differentiation process, in- cluding formation of acinar-like structures, production and **basal** deposition of basement **membrane** components, and production and apical secretion of sialomucins. Cell lines and cultures from human breast carcinomas failed to recapitulate this process. The data indicate the importance of cellular interactions with the basement membrane in the regulation of normal breast differentiation and, potentially, its loss in neoplasia. Purpose: Our purpose was to use this assay to investigate the role of the putative **metastasis** suppressor gene nm23-H1 in mammary development and differentiation. Methods: The metastatic human breast carcinoma cell line MDA-MB-435, clones transfected with a control pCMVBamneo vector, and clones transfected with pCMVBamneo vector containing nm23-H1 complementary DNA (the latter of which exhibited a substantial reduction in spontaneous metastatic potential in vivo) were cultured within a reconstituted basement membrane. Clones were ex- amined for formation of acinus-like spheres, deposition of basement membrane components, production of sialomucin, polarization, and growth arrest. Results: In contrast to the parental cell line and control transfectants, MDA-MB-435 breast carcinoma cells overexpressing Nm23-H1 protein regained several aspects of the normal phenotype within reconstituted basement membrane. Nm23-H1 protein-positive cells formed organized acinus-like spheres, deposited the basement membrane components type IV collagen and, to some extent, laminin to the outside of the spheres, expressed sialomucin, and growth arrested. Growth arrest of Nm23-H1 protein-positive cells was preceded by and correlated with formation of a basement membrane, suggesting a causal relationship. Conclusion: The data indicate a previously unidentified cause- and-effect relationship between nm23-H1 gene expression and morphological- biosynthetic-growth aspects of breast differentiation in this model system. Implications: While the basement membrane microenvironment is capable of directing the differentiation of normal human breast cells, neoplastic transformation abrogates this relationship, suggesting that intrinsic cellular events are also critical to this process. The data identify nm23-H1 gene expression as one of these events, suggesting an important role in the modulation of cellular responsiveness to the microenvironment. The data also identify previously unknown growth inhibitory effects of nm23-H1 gene overexpression.

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ACCESSION NUMBER: 94063810 EMBASE
DOCUMENT NUMBER: 1994063810
TITLE: Tyrosinase-induced phenoxyl radicals of etoposide (VP-16): Interaction with reductants in model systems, K562 leukemic cell and nuclear homogenates.
AUTHOR: Stoyanovsky D.; Yalowich J.; Gantchev T.; Kagan V.
CORPORATE SOURCE: Dept Environ and Occupational Health, University of Pittsburgh, 260 Kappa Drive,RIDC Park, Pittsburgh, PA 15238, United States
SOURCE: Free Radical Research Communications, (1993) 19/6 (371-386).
ISSN: 8755-0199 CODEN: FRRCEX
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
025 Hematology

030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

L55 ANSWER 79 OF 80 WPIX COPYRIGHT 2003 THOMSON DERWENT on STN
ACCESSION NUMBER: 1990-266209 [35] WPIX
DOC. NO. CPI: C1990-115330
TITLE: 1,5-Benzothiazepine ester derivs. - prepd. by reacting benzothiazepine deriv. with carboxylic acid in the presence of an inert solvent.
DERWENT CLASS: B02
PATENT ASSIGNEE(S): (ICHI-N) SHIN-ICHIRO SHIMIZU
COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
JP 02188574	A	19900724	(199035)*		

PRIORITY APPLN. INFO: JP 1989-7000 19890114
AB JP 02188574 A UPAB: 19930928
1,5-Benzothiazepine ester derivs. of formula (I) or their acid addn. salts are new: where R1 = lower alkyl or lower alkoxy; R2 = H or halogen; R3 and R4 = lower alkyl; n = 2 or 3; R5 = acyl gp. selected from **thioctic acid**, linolic acid, alpha-linolenic acid, 5,8,11,14,17-eicosapentaenoic acid, 4,7,10,13,16,19-docosahexaenoic acid, 6,9,12,15-octadecatetraenoic acid and palmitoleic acid; X is R5 or H.

Pref. (I) can be prepd. from cpds. of formula (II) (i.e., if X is H in formula (I)) on reaction with a carboxylic acid R5OH or its reactive deriv. (e.g., acid halide, acid anhydride). The reaction with the reactive deriv. may be carried out in an inert organic solvent, e.g., CH2Cl2, CHCl3, THF, dioxane, MeCN, EtOAc, DMFA, at a temp. of -10 to 80 deg.C, if required in presence of a deacidifying agent, e.g., pyridine, picoline, Et3N, K2CO3, Na2CO3, NaHCO3. When the free carboxylic acid is used, the reaction is carried out in presence of a condensing agent, e.g., DCC, carbonyldiimidazole, Vilsmeier reagent, in a solvent, e.g., CH2Cl2, CHCl3, THF, dioxane, MeCN, acetone, EtOAc, DMFA.

USE - (I) are effective in treatment of arteriosclerosis and hyperlipaemia, partic. cerebral arteriosclerosis, cerebral infarct, dementia, angina pectoris or myocardial infarction. Also effective in prevention of **metastasis** of tumours. (I) may be administered orally as tablets, pills, capsules, granules, powder, suppositories (sic), suspension or emulsion at a single or divided doses of 0.01-20 mg/kg a day.
0/0

L55 ANSWER 80 OF 80 EMBASE COPYRIGHT 2003 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 74019908 EMBASE
DOCUMENT NUMBER: 1974019908
TITLE: The reaction of 3 ethoxy 2 oxobutyraldehyde bis(thiosemicarbazonato) copper(II) with thiols.
AUTHOR: Petering D.H.
CORPORATE SOURCE: Dept. Chem., Northwest. Univ., Evanston, Ill. 60201, United

States
SOURCE: Bioinorganic Chemistry, (1972) 2/4 (273-288).
CODEN: BICHBX
DOCUMENT TYPE: Journal
FILE SEGMENT: 037 Drug Literature Index
029 Clinical Biochemistry
030 Pharmacology
LANGUAGE: English

Part II - no reference to alpha lipoic acid

FILE 'HCAPLUS' ENTERED AT 16:01:56 ON 26 NOV 2003
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE COVERS 1907 - 26 Nov 2003 VOL 139 ISS 22
FILE LAST UPDATED: 25 Nov 2003 (20031125/ED)

This file contains CAS Registry Numbers for easy and accurate
substance identification.

=> d que l9
L7 3157 SEA FILE=HCAPLUS ABB=ON PLU=ON METASTAS? AND CELL?(5A)ADHES?

L8 63 SEA FILE=HCAPLUS ABB=ON PLU=ON L7 AND BASAL?
L9 28 SEA FILE=HCAPLUS ABB=ON PLU=ON (BAC OR DMA OR PAC OR PKT OR
THU)/RL AND L8

=> b medline
FILE 'MEDLINE' ENTERED AT 16:02:04 ON 26 NOV 2003

FILE LAST UPDATED: 25 NOV 2003 (20031125/UP). FILE COVERS 1958 TO DATE.

On April 13, 2003, MEDLINE was reloaded. See HELP RLOAD for details.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the
MeSH 2003 vocabulary. See http://www.nlm.nih.gov/mesh/changes2003.html
for a description on changes.

This file contains CAS Registry Numbers for easy and accurate
substance identification.

=> d que l20
L18 3369 SEA FILE=MEDLINE ABB=ON PLU=ON METASTAS? AND CELL?(3A)ADHES?

L20 13 SEA FILE=MEDLINE ABB=ON PLU=ON L18 AND BASAL(3A)MEMBRANE

=> b embase
FILE 'EMBASE' ENTERED AT 16:02:10 ON 26 NOV 2003

FILE COVERS 1974 TO 20 Nov 2003 (20031120/ED)

EMBASE has been reloaded. Enter HELP RLOAD for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

```
=> d que l38
L35          3234 SEA FILE=EMBASE ABB=ON  PLU=ON  METASTAS? AND CELL?(3A)ADHES?
L38             9 SEA FILE=EMBASE ABB=ON  PLU=ON  L35 AND BASAL?(3A)MEMBRANE


=> b biosis drugu ipa wpix
FILE 'BIOSIS' ENTERED AT 16:02:19 ON 26 NOV 2003
COPYRIGHT (C) 2003 BIOLOGICAL ABSTRACTS INC.(R)

FILE 'DRUGU' ENTERED AT 16:02:19 ON 26 NOV 2003
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FILE 'IPA' ENTERED AT 16:02:19 ON 26 NOV 2003
COPYRIGHT (C) 2003 American Society of Hospital Pharmacists (ASHP)

FILE 'WPIX' ENTERED AT 16:02:19 ON 26 NOV 2003
COPYRIGHT (C) 2003 THOMSON DERWENT

=> d que l45
L45            11 SEA METASTAS? AND CELL(3A) ADHES? AND BASAL(3A) MEMBRAN?


=> dup rem l20 l9 l38 l45
FILE 'MEDLINE' ENTERED AT 16:02:32 ON 26 NOV 2003

FILE 'HCAPLUS' ENTERED AT 16:02:32 ON 26 NOV 2003
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COPYRIGHT (C) 2003 BIOLOGICAL ABSTRACTS INC.(R)

FILE 'WPIX' ENTERED AT 16:02:32 ON 26 NOV 2003
COPYRIGHT (C) 2003 THOMSON DERWENT
PROCESSING COMPLETED FOR L20
PROCESSING COMPLETED FOR L9
PROCESSING COMPLETED FOR L38
PROCESSING COMPLETED FOR L45
L56            45 DUP REM L20 L9 L38 L45 (16 DUPLICATES REMOVED)

=> d his

     (FILE 'HOME' ENTERED AT 15:04:15 ON 26 NOV 2003)

     FILE 'REGISTRY' ENTERED AT 15:04:21 ON 26 NOV 2003
L1             11 S .ALPHA.-LIPOIC ACID?/CN
```

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     FILE 'HCAPLUS' ENTERED AT 15:05:30 ON 26 NOV 2003
L2          551 S L1(L)(BAC OR DMA OR PAC OR PKT OR THU)/RL
                E ANTITUMOR AGENTS/CT
                E E3+OLD/CT
L3       165198 S ANTITUMOR AGENTS+OLD/CT
L4           31 S L2 AND L3
L5            4 S L2 AND METASTAS?
L6            4 S L2 AND CELL?(3A)ADHES?
L7         3157 S METASTAS? AND CELL?(5A)ADHES?
L8           63 S L7 AND BASAL?
L9           28 S (BAC OR DMA OR PAC OR PKT OR THU)/RL AND L8

     FILE 'MEDLINE' ENTERED AT 15:19:45 ON 26 NOV 2003
L10         291 S L1
                E ANTINEOPLAS/CT
                E E8+ALL
L11       80505 S ANTINEOPLASTIC AGENTS/CT
L12           0 S L10 AND L11
                E LIPOIC ACID/CT
                E E3+ALL
                E E2+ALL
L13        1299 S THIOCTIC ACID/CT
L14           6 S L13 AND L11
L15           6 S (L10 OR L13) AND L11
L16           1 S (L10 OR L13) AND METASTAS?
L17           6 S (L10 OR L13) AND CELL?(3A)ADHES?
L18        3369 S METASTAS? AND CELL?(3A)ADHES?
L19          85 S L18 AND BASAL
L20          13 S L18 AND BASAL(3A)MEMBRANE
L21          82 S L19 AND (CANCER? OR NEOPLAS? OR TUMOR?)

     FILE 'EMBASE' ENTERED AT 15:26:19 ON 26 NOV 2003
                E LIPOIC ACID/CT
                E E3+ALL
                E E2+ALL
L22        1570 S THIOCTIC ACID/CT
L23        1661 S (L1 OR L22)
                E ANTINEOPLAS/CT
L24       52028 S ANTINEOPLASTIC AGENT/CT
L25           9 S L23 AND L24
                E METASTASIS/CT
                E E3+ALL
L26       53893 S METASTASIS/CT
L27           1 S L23 AND L26
L28           1 S L23 AND METASTAS?
L29          26 S L23 AND BASAL?
                E BASAL MEMBRANE/CT
                E E3+ALL
                E E2+ALL
L30       12229 S BASEMENT MEMBRANE+NT/CT
L31           1 S L23 AND L30
L32           0 S L23 AND CELL?(5A)ADHES? AND BASAL?
L33           6 S L23 AND CELL?(5A)ADHES?
L34           7 S L31 OR L33
L35        3234 S METASTAS? AND CELL?(3A)ADHES?
L36          91 S L35 AND BASAL?
L37          85 S L36 AND (NEOPLAS? OR CANCER? OR TUMOR?)
```

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L38          9 S L35 AND BASAL?(3A)MEMBRANE

     FILE 'BIOSIS, DRUGU, IPA, WPIX' ENTERED AT 15:33:21 ON 26 NOV 2003
L39       2836 S L1 OR THIOCTIC ACID OR LIPOIC ACID
L40         68 S L39 AND (ANTITUMOR OR ANTINEOPLAS? OR ANTITUMOUR? OR ANTI()(T
L41         12 S L40 AND THERAPEUT?
L42          7 S L39 AND METASTAS?
L43         16 S L39 AND CELL?(3A)ADHES?
L44          0 S L43 AND BASAL?
L45         11 S METASTAS? AND CELL(3A)ADHES? AND BASAL(3A)MEMBRAN?

     FILE 'HCAPLUS' ENTERED AT 15:39:27 ON 26 NOV 2003
L46         63 S L4 OR L5 OR L6 OR L9

     FILE 'MEDLINE' ENTERED AT 15:40:44 ON 26 NOV 2003
L47         26 S L15 OR L16 OR L17 OR L20

     FILE 'EMBASE' ENTERED AT 15:41:39 ON 26 NOV 2003

     FILE 'BIOSIS, DRUGU, IPA, WPIX' ENTERED AT 15:42:24 ON 26 NOV 2003

     FILE 'EMBASE' ENTERED AT 15:42:36 ON 26 NOV 2003
L48         26 S L25 OR L27 OR L34 OR L38

     FILE 'BIOSIS, DRUGU, IPA, WPIX' ENTERED AT 15:43:11 ON 26 NOV 2003
L49         34 S L42 OR L43 OR L45

     FILE 'MEDLINE, HCAPLUS, EMBASE, BIOSIS, DRUGU, WPIX' ENTERED AT 15:43:54
     ON 26 NOV 2003
L50        119 DUP REM L47 L46 L48 L49 (30 DUPLICATES REMOVED)

     FILE 'HCAPLUS' ENTERED AT 15:49:08 ON 26 NOV 2003
L51         35 S L4 OR L5 OR L6

     FILE 'MEDLINE' ENTERED AT 15:49:45 ON 26 NOV 2003
L52         13 S L15 OR L16 OR L17

     FILE 'EMBASE' ENTERED AT 15:50:15 ON 26 NOV 2003
L53         19 S L25 OR L27 OR L38

     FILE 'BIOSIS, DRUGU, IPA, WPIX' ENTERED AT 15:58:50 ON 26 NOV 2003
L54         23 S L42 OR L43

     FILE 'MEDLINE, HCAPLUS, EMBASE, BIOSIS, DRUGU, WPIX' ENTERED AT 15:59:26
     ON 26 NOV 2003
L55         80 DUP REM L52 L51 L53 L54 (10 DUPLICATES REMOVED)

     FILE 'HCAPLUS' ENTERED AT 16:01:56 ON 26 NOV 2003

     FILE 'MEDLINE' ENTERED AT 16:02:04 ON 26 NOV 2003

     FILE 'EMBASE' ENTERED AT 16:02:10 ON 26 NOV 2003

     FILE 'BIOSIS, DRUGU, IPA, WPIX' ENTERED AT 16:02:19 ON 26 NOV 2003

     FILE 'MEDLINE, HCAPLUS, EMBASE, BIOSIS, WPIX' ENTERED AT 16:02:32 ON 26
     NOV 2003
```

L56 45 DUP REM L20 L9 L38 L45 (16 DUPLICATES REMOVED)

=> s l56 not (l51 or l52 or l53 or l54)
'RL' IS NOT A VALID FIELD CODE
RELATIONSHIP 'OLD' IGNORED
NOT A VALID RELATIONSHIP CODE FOR FIELD 'CT'
2 FILES SEARCHED...
<------User Break------>

SEARCH ENDED BY USER

=> s l56 not l55
L57 42 L56 NOT L55

=> d l57 ibib ab 1-42

L57 ANSWER 1 OF 42 MEDLINE on STN
ACCESSION NUMBER: 2003347973 MEDLINE
DOCUMENT NUMBER: 22762204 PubMed ID: 12879601
TITLE: [Expression of **cell adhesion** molecules E-cadherin and beta-catenin in infiltrating breast carcinoma].
Ekspressiia molekul mezhkletochnoi adgezii E-kadkherina i beta-katenina v infil'trativnykh kartsinomakh molochnoi zhelezy.
AUTHOR: Chipysheva T A; Gel'shtein V I; Ermilova V D; Vishnevskaia Ia V; Vasil'ev Iu M
CORPORATE SOURCE: N. N. Blokhin Cancer Research Center, 115478, Moscow.
SOURCE: ARKHIV PATOLOGII, (2003 May-Jun) 65 (3) 3-7.
Journal code: 0370604. ISSN: 0004-1955.
PUB. COUNTRY: Russia: Russian Federation
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Russian
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200309
ENTRY DATE: Entered STN: 20030726
Last Updated on STN: 20030923
Entered Medline: 20030922

AB Distribution of **cell-cell adhesion** molecules of E-cadherin (EC) and beta-catenin (BC) infiltrating breast carcinoma (BC) and markers of epithelium, **basal membrane** has been studied by immunofluorescence in 50 infiltrating BC tissue samples including 17 ductal carcinomas, 23 lobular carcinomas and 10 combined carcinomas. Two types of EC-BC structure alterations were found: homogeneity disorder accompanied by appearance of local thickening and gaps or complete lack of these structures. Alterations of type 1 were found in all the analyzed samples of ductal and combined carcinomas and partially in lobular carcinomas, in in situ structures and in invasion components as well. Alterations of type 2 were found in 16 cases of lobular carcinomas of 23 examined. Our data suggest the existence of two groups of lobular BC: carcinomas with partial depletion of EC-BC structures and carcinomas which lost these structures. Further investigations are needed to evaluate clinical importance of the difference found.

L57 ANSWER 2 OF 42 MEDLINE on STN
ACCESSION NUMBER: 2003145256 MEDLINE

DOCUMENT NUMBER: 22547370 PubMed ID: 12660814
TITLE: Subtractive immunization using highly metastatic human tumor cells identifies SIMA135/CDCP1, a 135 kDa cell surface phosphorylated glycoprotein antigen.
AUTHOR: Hooper John D; Zijlstra Andries; Aimes Ronald T; Liang Hongyan; Claassen Gisela F; Tarin David; Testa Jacqueline E; Quigley James P
CORPORATE SOURCE: Department of Cell Biology, The Scripps Research Intitute, La Jolla, CA 92037, USA.
CONTRACT NUMBER: CA65660 (NCI)
HL31950 (NHLBI)
T32 HL07195 (NHLBI)
T32 HL07695 (NHLBI)
SOURCE: ONCOGENE, (2003 Mar 27) 22 (12) 1783-94.
Journal code: 8711562. ISSN: 0950-9232.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200304
ENTRY DATE: Entered STN: 20030328
Last Updated on STN: 20030417
Entered Medline: 20030416

AB We have previously used a subtractive immunization (SI) approach to generate monoclonal antibodies (mAbs) against proteins preferentially expressed by the highly metastatic human epidermoid carcinoma cell line, M(+)HEp3. Here we report the immunopurification, identification and characterization of SIMA135/CDCP1 (subtractive immunization M(+)HEp3 associated 135 kDa protein/CUB domain containing protein 1) using one of these mAbs designated 41-2. Protein expression levels of SIMA135/CDCP1 correlated with the metastatic ability of variant HEp3 cell lines. Protein sequence analysis predicted a cell surface location and type I orientation of SIMA135/CDCP1, which was confirmed directly by immunocytochemistry. Analysis of deglycosylated cell lysates indicated that up to 40 kDa of the apparent molecular weight of SIMA135/CDCP1 is because of N-glycosylation. Western blot analysis using a antiphosphotyrosine antibody demonstrated that SIMA135/CDCP1 from HEp3 cells is tyrosine phosphorylated. Selective inhibitor studies indicated that an Src kinase family member is involved in the tyrosine phosphorylation of the protein. In addition to high expression in M(+)HEp3 cells, the SIMA135/CDCP1 protein is expressed to varying levels in 13 other human tumor cell lines, manifesting only a weak correlation with the reported metastatic ability of these tumor cell lines. The protein is not detected in normal human fibroblasts and endothelial cells. Northern blot analysis indicated that SIMA135/CDCP1 mRNA has a restricted expression pattern in normal human tissues with highest levels of expression in skeletal muscle and colon. Immunohistochemical analysis indicated apical and **basal** plasma **membrane** expression of SIMA135/CDCP1 in epithelial cells in normal colon. In colon tumor, SIMA135/CDCP1 expression appeared dysregulated showing extensive cell surface as well as cytoplasmic expression. Consistent with in vitro shedding experiments on HEp3 cells, SIMA135/CDCP1 was also detected within the lumen of normal and cancerous colon crypts, suggesting that protein shedding may occur in vivo. Thus, specific immunodetection followed by proteomic analysis allows for the identification and partial characterization of a heretofore uncharacterized human cell surface antigen.

L57 ANSWER 3 OF 42 MEDLINE on STN
ACCESSION NUMBER: 2000331006 MEDLINE
DOCUMENT NUMBER: 20331006 PubMed ID: 10872246
TITLE: [Molecular genetic principles of progression of malignant diseases].
Molekulargenetische Grundlagen der Progression maligner Erkrankungen.
AUTHOR: Wullich B
CORPORATE SOURCE: Klinik und Poliklinik fur Urologie und Kinderurologie, Universitat des Saarlandes, Homburg/Saar.
SOURCE: UROLOGE. AUSGABE A, (2000 May) 39 (3) 222-7. Ref: 5
Journal code: 1304110. ISSN: 0340-2592.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: German
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200008
ENTRY DATE: Entered STN: 20000811
Last Updated on STN: 20000811
Entered Medline: 20000801

AB During the past decade, the molecular mechanisms in the process of tumor progression, including **metastasis** and angiogenesis, have become better understood. Cancer **metastasis** consists of multiple, complex interacting steps. Each of these steps is crucial and limiting, since a failure to complete any one prevents the tumor cell from producing a **metastasis**. Detachment from the solid tumor by loosening the intercellular junctions and proteolysis of the extracellular matrix enables tumor cells to enter blood- and lymph vessels. The intravasation into the circulation is supported by the secretion of angiogenic factors, which induce degradation of the **basal membrane** in blood vessels. **Adhesion** to endothelial **cells**, extravasation from the circulation, and induction of angiogenesis are further essential steps for completing the metastatic process. Furthermore, it is well known that once a tumor cell has entered circulation, it will survive only by evasion of the immune system. The systematic identification of tumor antigens opens up new possibilities for immunotherapeutic approaches.

L57 ANSWER 4 OF 42 MEDLINE on STN
ACCESSION NUMBER: 1999299930 MEDLINE
DOCUMENT NUMBER: 99299930 PubMed ID: 10372715
TITLE: Laminin receptors in differentiated thyroid tumors: restricted expression of the 67-kilodalton laminin receptor in follicular carcinoma cells.
AUTHOR: Montuori N; Muller F; De Riu S; Fenzi G; Sobel M E; Rossi G; Vitale M
CORPORATE SOURCE: Dipartimento di Biologia e Patologia Cellulare e Molecolare, Universita Federico II, Naples, Italy.. mavitale@cds.unina.it
SOURCE: JOURNAL OF CLINICAL ENDOCRINOLOGY AND METABOLISM, (1999 Jun) 84 (6) 2086-92.
Journal code: 0375362. ISSN: 0021-972X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199907
ENTRY DATE: Entered STN: 19990715
Last Updated on STN: 19990715
Entered Medline: 19990702

AB The expression of integrin laminin receptors was investigated in normal thyroid primary cultures; immortalized normal thyroid cells (TAD-2); papillary (NPA), follicular (WRO), and anaplastic (ARO) thyroid tumor cell lines; seven thyroid tumors (four papillary and three follicular carcinomas); and normal thyroid glands. The expression of alphalbeta1, alpha2beta1, alpha3beta1, alpha6beta1, and alpha6beta4 was found in all tumor specimens and in tumor cell lines, whereas normal thyroid cells and TAD-2 cells lacked the expression of alpha6beta4. Despite the presence of several integrin laminin receptors, adhesion of TAD-2, NPA, and ARO cells to immobilized laminin-1 was poor, whereas WRO cells and follicular carcinoma-derived **cells** displayed a strong **adhesion**. Indeed, WRO and follicular carcinoma-derived cells showed expression of a nonintegrin laminin receptor, the 67-kDa high affinity laminin receptor (67LR). TAD-2, NPA, and ARO cells as well as nodular goiter, toxic adenoma, follicular adenoma, and papillary carcinoma-derived cells did not express the 67LR. Adhesion of WRO and follicular carcinoma-derived cells to laminin-1 was specifically inhibited by a recombinant polypeptide containing laminin-binding domains of 67LR, demonstrating that this receptor confers to follicular carcinoma cells attachment capacity to laminin. Moreover, tissue specimens from follicular carcinomas expressed the 67LR, whereas follicular adenomas and normal thyroid tissues were negative. In thyroid tumors, integrin receptors, although abundant, participate weakly in adhesion to laminin. The expression in follicular carcinoma cells of a functional, high affinity 67LR together with nonfunctional integrin LM receptors could be responsible for the tendency of follicular carcinoma cells to **metastasize** by mediating stable contacts with **basal membranes**.

L57 ANSWER 5 OF 42 MEDLINE on STN
ACCESSION NUMBER: 1999140412 MEDLINE
DOCUMENT NUMBER: 99140412 PubMed ID: 10048983
TITLE: Integrin alpha6beta1 role in metastatic behavior of human pancreatic carcinoma cells.
AUTHOR: Vogelmann R; Kreuser E D; Adler G; Lutz M P
CORPORATE SOURCE: Department of Internal Medicine I, University of Ulm, Germany.
SOURCE: INTERNATIONAL JOURNAL OF CANCER, (1999 Mar 1) 80 (5) 791-5. Journal code: 0042124. ISSN: 0020-7136.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199902
ENTRY DATE: Entered STN: 19990311
Last Updated on STN: 19990311
Entered Medline: 19990225

AB The factors that determine the metastatic behavior of pancreatic tumor cells are incompletely understood. In this study, we first demonstrate differences in adhesion properties, integrin expression and in vivo integrin function in the metastatic tumor cell line PaTu 8988s compared with the non-metastatic cell line PaTu 8988t. Both cell lines were

derived from the same original tumor and exhibit identical genetic fingerprints. Using in vitro adhesion assays performed on purified extracellular matrix components, **adhesion** of PaTu 8988s **cells** was significantly increased on the **basal membrane** component laminin and decreased on the interstitial matrix protein fibronectin compared to PaTu 8988t cells. By immunocytochemistry and flow cytometry, and in correspondence with their adhesive properties, the metastatic PaTu 8988s cells did express a distinct pattern of integrin subunits. Laminin-binding integrins alpha6 and beta4 were overexpressed in PaTu 8988s cells. Fibronectin-binding alpha5 integrins were present at higher levels in the non-metastatic PaTu 8988t cells, whereas the beta1 subunit expression did not differ. Adhesion to laminin or fibronectin was specific and was mediated via integrins alpha6beta1 and alpha5beta1, respectively. In addition, **metastasis** formation in vivo after injection of cells into the tail vein of nude mice was inhibited by preincubation of PaTu 8988s cells with antibodies directed against the integrin alpha6 or beta1. We conclude that alpha6beta1 integrins are overexpressed and functionally active in metastatic human pancreatic carcinoma cells, and participate in **metastasis** formation probably through binding to the **basal membrane** component laminin.

L57 ANSWER 6 OF 42 MEDLINE on STN
ACCESSION NUMBER: 1999080748 MEDLINE
DOCUMENT NUMBER: 99080748 PubMed ID: 9863380
TITLE: [Adhesion molecules in kidney diseases (part I)]. Adhezioni molekuli u bolestima bubrega (I deo).
AUTHOR: Markovic-Lipkovski J; Basta-Jovanovic G; Smiljanic-Radotic K
CORPORATE SOURCE: Institute of Pathology, University School of Medicine, Belgrade.
SOURCE: SRPSKI ARHIV ZA CELOKUPNO LEKARSTVO, (1998 May-Jun) 126 (5-6) 192-6. Ref: 12
Journal code: 0027440. ISSN: 0370-8179.
PUB. COUNTRY: Yugoslavia
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: Serbo-Croatian
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199901
ENTRY DATE: Entered STN: 19990202
Last Updated on STN: 19990202
Entered Medline: 19990120

AB Adhesive molecules are (glyco)proteins of the cellular membranes. All of them have their extramembranous, transmembranous and intracytoplasmatic parts. As receptor molecules, their extracellular parts bind the specific ligand. The ligand can be found on the surface of the other cell or in the extracellular matrix (**basal membranes**). The following families of adhesion molecules are: cadherins, selectins, integrins and members of immunoglobuline supergene family. Different members of the same family could have different times (in ontogenesis, in adult form) and space distribution (in different tissues, different tissue structures). The contact between the cells and **basal membranes** with these molecules is important for cell division, maintaining the tissue architecture, polarization and function of cells, migration of cells, endo- and exo-cytosis as well as for maintaining the

structure and function of **basal membranes**. As above stated all this is important in the occurrence morphogenesis, haemostasis, inflammation, malignant cell transformation and **metastasis**. This knowledge is important for the better understanding of renal diseases.

L57 ANSWER 7 OF 42 MEDLINE on STN
ACCESSION NUMBER: 1998268346 MEDLINE
DOCUMENT NUMBER: 98268346 PubMed ID: 9607330
TITLE: How platelet aggregation affects B16BL6 melanoma cell trafficking.
AUTHOR: Koike C; Watanabe M; Isoai A; Kumagai H; Tsukada H; Irimura T; Okada S; Oku N
CORPORATE SOURCE: School of Pharmaceutical Sciences, University of Shizuoka, Japan.
SOURCE: FEBS LETTERS, (1998 May 8) 427 (2) 286-90.
Journal code: 0155157. ISSN: 0014-5793.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199806
ENTRY DATE: Entered STN: 19980625
Last Updated on STN: 19980625
Entered Medline: 19980618

AB In blood-borne **metastasis**, intravasated metastatic tumor cells are thought to localize at the target site via a series of processes involving platelet aggregation, adhesion to endothelium, and invasion through the **basal membrane**. In the present study, we examined how platelet aggregation contributes to the trafficking of metastatic tumor cells in vivo by use of an inhibitor of platelet aggregation. Highly invasive B16BL6 melanoma cells were labeled with [2-18F]2-fluoro-2-deoxy-D-glucose and injected into mice to determine cell trafficking non-invasively by positron emission tomography. Both platelet aggregation inhibitor cyclo(RSarDPhg), which could not inhibit **metastasis**, and metastatic inhibitor cyclo(GRGDSPA) suppressed the accumulation of B16BL6 cells in the lung by about 12%, suggesting that platelet aggregation partly affects cell trafficking but not to a great extent, and that platelet aggregation is not the essential step for B16BL6 cell arrest in targets.

L57 ANSWER 8 OF 42 MEDLINE on STN
ACCESSION NUMBER: 1998260373 MEDLINE
DOCUMENT NUMBER: 98260373 PubMed ID: 9598011
TITLE: Abnormal expression of epiligrin and alpha 6 beta 4 integrin in basal cell carcinoma.
AUTHOR: Schofield O; Kist D; Lucas A; Wayner E; Carter W; Zachary C
CORPORATE SOURCE: Department of Dermatology, University of Minnesota Hospital and Clinic, Minneapolis, USA.
SOURCE: DERMATOLOGIC SURGERY, (1998 May) 24 (5) 555-9.
Journal code: 9504371. ISSN: 1076-0512.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199806
ENTRY DATE: Entered STN: 19980618

Last Updated on STN: 20000303
Entered Medline: 19980610

AB BACKGROUND: Basal cell carcinoma is characterized by local invasion, and only rarely **metastasizes**. The role of the containing basement membrane (BM) in this tumor is unclear. Several BM components have been shown to be absent or significantly reduced in BM surrounding infiltrating tumor. OBJECTIVE: The purpose of this study is to examine the expression of epiligrin, a BM-associated glycoprotein, and the integrin chains alpha 3, alpha 6, beta 1, and beta 4 in the basement **membranes** surrounding **basal** cell carcinoma. METHODS: Samples were obtained from 20 patients with basal cell carcinomas and subjected to a standard avidin biotin complex/alkaline phosphatase immunohistochemical technique using a panel of antibodies. RESULTS: There was a consistent abnormality of expression of epiligrin, alpha 6, and beta 4. CONCLUSION: We propose that reduced expression of epiligrin is involved in the pathogenesis of the local invasion by tumor and that an altered integrin ratio in basal cell carcinoma enhances tumor spread.

L57 ANSWER 9 OF 42 MEDLINE on STN
ACCESSION NUMBER: 96396475 MEDLINE
DOCUMENT NUMBER: 96396475 PubMed ID: 8803595
TITLE: Expression of adhesion molecules and extracellular matrix proteins in glioblastomas: relation to angiogenesis and spread.
AUTHOR: Vitolo D; Paradiso P; Uccini S; Ruco L P; Baroni C D
CORPORATE SOURCE: Department of Experimental Medicine and Pathology, University La Sapienza Roma, Italy.
SOURCE: HISTOPATHOLOGY, (1996 Jun) 28 (6) 521-8.
Journal code: 7704136. ISSN: 0309-0167.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199612
ENTRY DATE: Entered STN: 19970128
Last Updated on STN: 19970128
Entered Medline: 19961219

AB We studied the immunohistochemical expression of inducible adhesion molecules, integrins and extracellular matrix proteins in 10 cases of glioblastoma multiforme in order to investigate their angiogenesis, local invasiveness, poor **metastasizing** properties and their lack of tumour infiltrating leukocytes. In glioblastomas endothelial proliferations represent the majority of vascular structures; they were positive for endothelial markers (vWF, CD31, VE-cadherin) and negative for macrophage markers (CD68, PAM-1). Immunohistologically, they were subtyped into: 1 solid-glomeruloid ICAM-1, alpha 2 beta 1, alpha 3 beta 1, alpha 5 beta 1 negative; 2 channelled-branching ICAM-1 negative and alpha 2 beta 1, alpha 3 beta 1, alpha 5 beta 1 positive; 3 channelled-telangiectatic ICAM-1, alpha 2 beta 1, alpha 3 beta 1, alpha 5 beta 1 positive. In channelled proliferations, the expression and distribution of tenascin and merosin in the **basal membrane** was similar to that of normal brain vessels. The expression of all these molecules might indicate different steps of maturation of endothelial proliferations. The majority of endothelial proliferations may be immunohistologically considered as incomplete vascular structures; this might account for the low **metastasizing** tendency and low recruitment of leukocytes by these tumours. Neoplastic astrocytes were

GFAP-1, ICAM-1, VCAM-1, alpha 2 beta 1, alpha 3 beta 1 and alpha 5 beta 1 immunoreactive and alpha 6 beta 4 negative: this allows them to interact with extracellular matrix proteins and might, in part, explain the tendency of glioblastomas to infiltrate locally.

L57 ANSWER 10 OF 42 MEDLINE on STN
ACCESSION NUMBER: 96159046 MEDLINE
DOCUMENT NUMBER: 96159046 PubMed ID: 8567400
TITLE: Inhibition of tumor cell haptotaxis by sodium D-glucaro-delta-lactam (ND2001).
AUTHOR: Tsuruoka T; Azetaka M; Iizuka Y; Saito K; Inouye S; Hosokawa M; Kobayashi H
CORPORATE SOURCE: Pharmaceutical Research Center, Meiji Seika Kaisha, Ltd., Yokohama.
SOURCE: JAPANESE JOURNAL OF CANCER RESEARCH, (1995 Nov) 86 (11) 1080-5.
Journal code: 8509412. ISSN: 0910-5050.
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199603
ENTRY DATE: Entered STN: 19960315
Last Updated on STN: 19970203
Entered Medline: 19960304

AB We used the Boyden chamber system to investigate the mechanism by which the antimetastatic agent sodium D-glucaro-delta-lactam (ND2001) inhibits tumor cell invasion, and by establishing what ND2001 did not achieve, we were able to pinpoint the areas in which it was successful as an inhibitor. ND2001 did not inhibit **cell adhesion** of a highly metastatic B16 melanoma variant (the B16 variant) to the reconstituted **basal membrane** Matrigel, nor did it affect the production or activity of **basal membrane** -degrading type i.v. collagenase, but, in the Boyden chamber, ND2001 inhibited cell migration of the B16 variant toward a chemoattractant, laminin, on the lower surface of a Matrigel-free filter set (haptotaxis). Lewis lung carcinoma (3LL) cells that had been treated with ND2001 also exhibited hardly any haptotaxis, although the cells showed no alteration in behavior during **cell adhesion** to Matrigel. Since ND2001 did succeed in inhibiting the pulmonary **metastases** of the B16 variant and 3LL, we infer that inhibition of the **metastases** by ND2001 in these tumors is likely to be due to the inhibition of haptotactic migration.

L57 ANSWER 11 OF 42 MEDLINE on STN
ACCESSION NUMBER: 95368331 MEDLINE
DOCUMENT NUMBER: 95368331 PubMed ID: 7543797
TITLE: Extracellular matrix proteins and VLA integrins expression in the microenvironment of human lung carcinoma.
AUTHOR: Zeromski J; Lawniczak M; Mizera-Nyczak E; Zocch[illegible] M R
CORPORATE SOURCE: Department of Immunopathology, University of Medical Sciences, Poznan.
SOURCE: POLISH JOURNAL OF PATHOLOGY, (1995) 46 (2) 63-9.
Journal code: 9437432. ISSN: 1233-9687.
PUB. COUNTRY: Poland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English

FILE SEGMENT: Priority Journals
ENTRY MONTH: 199509
ENTRY DATE: Entered STN: 19950930
Last Updated on STN: 19960708
Entered Medline: 19950921

AB In order to gain an insight into interactions between human cancer and the surrounding host tissues, surgical samples of lung carcinoma of distinct histological types were examined for the expression of extracellular matrix (ECM) proteins and very late antigen (VLA) integrins, by means of a panel of monoclonal antibodies and immunohistochemistry of frozen tissue sections. It has been found that fibronectin (FN), tenascin (TN) and to a lesser degree collagen IV were abundant in the immediate vicinity of the tumor, but only TN penetrated tumor mass. FN isoforms were scarce or undetectable within the tumor area. The walls of blood vessels in the vicinity of the tumor showed increased an expression of collagen IV and laminin. The latter was occasionally absent within the **basal membrane** of cancer cells. The expression of EMC proteins was inversely proportional to the intensity of mononuclear tumor infiltrating cells (TIC). VLA integrins were present on both types of the cells: TIC and tumor cells. Percentage of positive TIC varied from 20% to 70%, depending on VLA integrin tested. VLA-3 was demonstrated on most of the cells of squamous carcinoma, but was almost absent on those of anaplastic small cell carcinoma one. In metastatic lymph node, VLA-4 was strongly expressed on tumor cells comparing to lymphoid ones. These data show that VLA integrins and their EMC ligands play apparently an important, but still obscure role in the interactions between lung carcinoma and its host.

L57 ANSWER 12 OF 42 MEDLINE on STN
ACCESSION NUMBER: 95363570 MEDLINE
DOCUMENT NUMBER: 95363570 PubMed ID: 7636625
TITLE: Altered expression and function of E-cadherin in cervical intraepithelial neoplasia and invasive squamous cell carcinoma.
AUTHOR: Vessey C J; Wilding J; Folarin N; Hirano S; Takeichi M; Soutter P; Stamp G W; Pignatelli M
CORPORATE SOURCE: Department of Histopathology, Royal Postgraduate Medical School, London, U.K.
SOURCE: JOURNAL OF PATHOLOGY, (1995 Jun) 176 (2) 151-9.
Journal code: 0204634. ISSN: 0022-3417.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199509
ENTRY DATE: Entered STN: 19950921
Last Updated on STN: 19950921
Entered Medline: 19950913

AB HECD-1 monoclonal antibody has been used to localize E-cadherin, a calcium-dependent **cell-cell adhesion** molecule, in microwave-treated, paraffin-embedded sections from 53 cases of cervical intraepithelial neoplasia (CIN) (11 CIN I, 22 CIN II, and 20 CIN III), 16 invasive cervical squamous cell carcinomas, and seven **metastases**. In normal cervix, E-cadherin was expressed on the cell **membrane** of **basal** and parabasal cells. Cytoplasmic staining was present in occasional basal cells only. In CIN, the presence and localization of cytoplasmic E-cadherin were found to be

significantly correlated with the grade of the CIN lesion. In squamous cell carcinomas, reduced membranous and increased cytoplasmic staining was seen with worsening differentiation. Loss of membranous E-cadherin expression was also detected in 4/7 metastatic deposits. E-cadherin expression (120 kD form on Western blotting) was seen in human cervical carcinoma cell lines (HT3, ME180, C4I, Caski) that maintained the ability to aggregate in a homotypic adhesion assay and showed a typical epithelial morphology. E-cadherin-negative cell lines (Hela, SiHa, C33A) did not show adhesion. HOG-1 was the only E-cadherin-negative cell line which showed a significant degree of cell-cell aggregation. These data indicate that loss of membranous E-cadherin expression may represent one of the abnormalities underlying loss of cell polarity and differentiation which characterize CIN and invasive cervical cancer.

L57 ANSWER 13 OF 42 MEDLINE on STN
ACCESSION NUMBER: 90115087 MEDLINE
DOCUMENT NUMBER: 90115087 PubMed ID: 2608328
TITLE: [Control of cell movement by laminin, multifunctional glycoprotein of the **basal membrane**. Role in **metastasis**].
Le controle du mouvement cellulaire par la laminine, une glycoproteine multifonctionnelle de la membrane basale. Role dans la **metastase**.
AUTHOR: Lissitzky J C; Bouzon M; Delori P; Martin P M
CORPORATE SOURCE: UA CNRS 201, Faculte de Medecine Nord, Marseille, France.
SOURCE: PATHOLOGIE BIOLOGIE, (1989 Nov) 37 (9) 1028-9.
Journal code: 0265365. ISSN: 0369-8114.
PUB. COUNTRY: France
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: French
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199002
ENTRY DATE: Entered STN: 19900328
Last Updated on STN: 19900328
Entered Medline: 19900222

L57 ANSWER 14 OF 42 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2003:118026 HCAPLUS
DOCUMENT NUMBER: 138:165525
TITLE: Crystal structure of NC1 domain hexamer of bovine type IV collagen and application to drug screening and drug design
INVENTOR(S): Sundaramoorthy, Muirathinam; Hudson, Billy
PATENT ASSIGNEE(S): University of Kansas Medical Center, USA
SOURCE: PCT Int. Appl., 168 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003012122	A2	20030213	WO 2002-US23763	20020726

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,

LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2003100510 A1 20030529 US 2002-206699 20020726
PRIORITY APPLN. INFO.: US 2001-308523P P 20010727
US 2001-351289P P 20011029
US 2002-366854P P 20020322
US 2002-385362P P 20020603

OTHER SOURCE(S): MARPAT 138:165525

AB The present invention provides a crystd. NC1 domain hexamer of bovine type IV collagen, and methods for making the crystal, wherein the NC1 domain hexamer is cystallized such that the three dimensional structure of the cystallized NC1 domain hexamer can be detd. to a resoln. of at least 3 .ANG. or better. The present invention also provides a method for designing compds. to inhibit angiogenesis, tumor growth, tumor **metastasis**, endothelial **cell adhesion** and/or proliferation, and/or **basal** lamina assembly, comprising analyzing the three dimensional structure of a cystallized type IV collagen NC1 domain hexamer produced by the methods of the invention, and identifying and synthesizing compds. that target regions of the NC1 domain that have been identified by the anal. as being important for type IV collagen heterotrimer and hexamer assembly. The present invention also provides novel polypeptides designed by the rational drug design methods of the present invention, based on an anal. of the type IV collagen NC1 hexamer structure disclosed herein.

L57 ANSWER 15 OF 42 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2003:117983 HCAPLUS
DOCUMENT NUMBER: 138:164859
TITLE: Gene expression profile of human prostate cancer and its use for cancer drug screens and therapeutic applications
INVENTOR(S): Rubin, Mark A.; Chinnaiyan, Arul M.; Sreekumar, Arun
PATENT ASSIGNEE(S): The Regents of the University of Michigan, USA
SOURCE: PCT Int. Appl., 297 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003012067	A2	20030213	WO 2002-US24567	20020802

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG,

CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2003175736 A1 20030918 US 2002-210120 20020801

PRIORITY APPLN. INFO.: US 2001-309581P P 20010802
US 2001-334468P P 20011115
US 2002-210120 A 20020801

AB The present invention relates to compns. and methods for cancer diagnostics, including but not limited to, cancer markers. In particular, the present invention provides gene expression profiles assocd. with prostate cancers. Genes up-regulated in prostate cancer are identified utilizing glass slide cDNA microarrays (Research Genetics 10K human cDNA microarray) that include .apprx.5000 known and named genes, 4400 ESTs, and 500 control elements. Expression of relevant genes is confirmed using Western blot anal. Two genes, hepsin and pim-1 are identified as genes that are of particular relevance: hepsin strains strongly in pre-cancerous tissue but less strongly in prostate cancer tissues of men found to have an increased risk of **metastasis**, and decreased expression of pim-1 in prostate cancer tissue is assocd. with increased risk of prostate cancer failure. .alpha.-Methyl-CoA racemase is expressed on prostate cancer, but not benign prostate hyperplasia. Further, EZH2 is up-regulated in metastatic prostate cancer relative to localized prostate cancer and benign tissue. Finally, annexins 1,2,4,7,11 are significantly decreased in hormone-refractory prostate cancer when compared to localized hormone-naive prostate cancer. Genes identified as cancer markers using the methods of the present invention find use in the diagnosis and characterization of prostate cancer. In addn., the genes provide targets for cancer drug screens and therapeutic applications.

L57 ANSWER 16 OF 42 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2001:322938 HCAPLUS
DOCUMENT NUMBER: 135:120429
TITLE: Laminin-10 Mediates **Basal** and EGF-Stimulated Motility of Human Colon Carcinoma Cells via .alpha.3.beta.1 and .alpha.6.beta.4 Integrins
AUTHOR(S): Pouliot, Normand; Nice, Edouard C.; Burgess, Antony W.
CORPORATE SOURCE: The Ludwig Institute for Cancer Research, Melbourne Branch, 3050, Australia
SOURCE: Experimental Cell Research (2001), 266(1), 1-10
CODEN: ECREAL; ISSN: 0014-4827
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Signals from the epidermal growth factor (EGF) receptor and integrin-dependent adhesion to laminin contribute to the progression and **metastasis** of colonic tumors. However, little is know about the mechanisms by which these signals cooperate. Recently, we have reported that the colon cancer cell line LIM1215 secretes and adhere to autocrine laminin-10 via multiple integrin receptors and that EGF stimulates spreading of these cells on the same substrate. In this report, we investigate the effect of EGF and laminin-10 on colon cancer cell migration in vitro. EGF stimulates migration of LIM1215 cells in a wound healing assay. The response to EGF is inhibited by anti-EGF receptor antibody 528, the EGF receptor kinase inhibitor AG-1478, or the MAP kinase inhibitor PD98059 but not the PI3-K inhibitor wortmannin. Using transwell migration chambers, we demonstrate that laminin-10 but not collagen-I, collagen-IV, or a com. prepn. of human placental laminin is a potent

motility factor for LIM1215 cells. The migration response to laminin-10 is increased upon stimulation of the cells with EGF and correlates with the up-regulation of .alpha.6.beta.4 integrin expression as measured by anal. of Triton X-100-sol. cellular exts. The results from integrin inhibition expts. indicate that **basal** migration on laminin-10 is mediated by .alpha.3.beta.1 but not .alpha.2.beta.1 nor .alpha.6.beta.4 integrins. .alpha.3 Blocking antibodies also inhibited EGF-stimulated chemokinetic migration of LIM1215 cells on laminin-10. However, in contrast to unstimulated cells, .alpha.6 or .beta.4 integrin-blocking antibodies inhibited the migration of EGF-stimulated cells by up to 50%. Taken together, these results support the cooperative role of EGF receptor and laminin-10 on colon cancer cell motility and suggest a crit. role for both the .alpha.3.beta.1 and the .alpha.6.beta.4 integrins in this process. (c) 2001 Academic Press.

REFERENCE COUNT: 61 THERE ARE 61 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L57 ANSWER 17 OF 42 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2000:896337 HCAPLUS
DOCUMENT NUMBER: 135:59210
TITLE: The pattern of expression of the 5T4 oncofoetal antigen on normal, dysplastic and malignant oral mucosa
AUTHOR(S): Ali, A.; Langdon, J.; Stern, P.; Partridge, M.
CORPORATE SOURCE: Maxillofacial Unit/Molecular Oncology, King's College Hospital, London, SE5 8RX, UK
SOURCE: Oral Oncology (2001), 37(1), 57-64
CODEN: EJCCER; ISSN: 1368-8375
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The human 5T4 oncofoetal antigen is expressed by all types of trophoblast in pregnancy but is not detected on most adult tissues, although low levels are found on some epithelia. However, this antigen is strongly expressed by many cancers and tumor-assocd. labeling correlates with metastatic spread and poor clin. outcome for patients with gastric and colon cancer. Over-expression of the gene influences **cell adhesion**, shape and motility, which may be related to changes in the cellular localization of the 5T4 oncofoetal antigen as malignancy develops. To establish whether the 5T4 oncofoetal antigen can serve as a tumor-specific marker for oral cancer and precancer, we have evaluated the pattern of expression on biopsies of normal, inflamed and dysplastic oral mucosa using immunohistochem. Oral mucosa, taken from different sites in the mouth, expressed the 5T4 oncofoetal antigen with varying intensity and pattern. The majority of the immunoreactivity was detected in the **basal** and suprabasal layers, with expression extending into the spinous cells at fully keratinised sites and when inflammation was present. This antigen was also detected in the underlying connective tissue. Oral squamous cell carcinoma showed a variety of patterns and intensity of staining corresponding to those found for normal mucosa. However, 21 of 41 cases showed no stromal labeling, a finding also obsd. for dysplastic lesions. The alterations in the pattern and intensity of 5T4 oncofoetal antigen expression were not related to clinicopathol. features of the tumors examd. These data show that the 5T4 oncofoetal antigen is expressed on normal oral mucosa, such that this target cannot be used for detection of neoplastic or preneoplastic cells, although altered expression may contribute to the pathogenesis of these lesions.

REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L57 ANSWER 18 OF 42 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2000:51180 HCAPLUS
DOCUMENT NUMBER: 132:329503
TITLE: Butyrate regulates E-cadherin transcription, isoform expression and intracellular position in colon cancer cells
AUTHOR(S): Barshishat, M.; Polak-Charcon, S.; Schwartz, B.
CORPORATE SOURCE: Institute of Biochemistry, Food Science and Nutrition, Faculty of Agricultural, Food and Environmental Quality Sciences, The Hebrew University of Jerusalem, Rehovot, 76100, Israel
SOURCE: British Journal of Cancer (2000), 82(1), 195-203
CODEN: BJCAAI; ISSN: 0007-0920
PUBLISHER: Churchill Livingstone
DOCUMENT TYPE: Journal
LANGUAGE: English
AB **Cell**-to-**cell adhesion**, an important event in differentiation, is impaired during advanced stages of tumorigenesis. In this study, we examd. the possible regulation of **cell-adhesion** proteins by the differentiation agent butyrate in LS174T and HM7 cells, two types of human colon cancer cells that differ in their ability to produce mucin and colonize the liver of exptl. animals. The more aggressive, high-mucin-producing cell line (HM7), a clone selected from LS174T cells, showed a scattered and undifferentiated ultramorphol. appearance and low **basal** alk. phosphatase activity; the proteins .beta.-catenin and E-cadherin, as detected by immunostaining, were expressed in the cells' nuclei. All of these properties were significantly less pronounced in the less aggressive, low-mucin-producing LS174T cells. In both cell lines, butyrate treatment enhanced cell-to-cell interaction, alk. phosphatase activity, translocation of .beta.-catenin and E-cadherin from the nuclei to the membrane junctions, and transcription and translation of the 120-kDa E-cadherin isoform, but not of its 100-kDa isoform. Anal. of possible mechanisms of E-cadherin up-regulation revealed that butyrate induces the release of nuclear proteins from the E-cadherin promoter sequence, reducing transcription repression. We suggest that butyrate activates E-cadherin transcription through translocation of nuclear transcription factors bearing specific repressor activity. We surmise that abrogation of nuclear 100-kDa E-cadherin and .beta.-catenin expression following butyrate treatment is related to the control of E-cadherin gene transcription.
REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L57 ANSWER 19 OF 42 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1999:785481 HCAPLUS
DOCUMENT NUMBER: 132:220427
TITLE: Expression of E-cadherin, .alpha.- & .beta.-catenin, and CD44V6 and the subcellular localization of E-cadherin and CD44V6 in normal epidermis and **basal** cell carcinoma
AUTHOR(S): Kooy, Angela J. W.; Tank, Bhupendra; de Jong, Anton A. W.; Vuzevski, Vojislav D.; van der Kwast, Theodorus H.; van Joost, Theodoor
CORPORATE SOURCE: Departments of Dermato-Venereology and Pathology,

Erasmus University Rotterdam, Rotterdam, 3000 DR, Neth.
SOURCE: Human Pathology (1999), 30(11), 1328-1335
CODEN: HPCQA4; ISSN: 0046-8177
PUBLISHER: W. B. Saunders Co.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB **Basal** cell carcinoma (BCC) of the skin is a locally invasive, rarely **metastasizing** epithelial tumor. In the current study, the expression of E-cadherin, .alpha.- and .beta.-catenin and CD44V6 in normal epidermis and on BCC cells were investigated. A significantly reduced expression of .alpha.-catenin and CD44V6 and a slightly reduced expression of E-cadherin on BCC cells were obsd. compared with the overlying epidermis. Immunoelectron microscopy was used to investigate whether the decreased expression of E-cadherin and CD44V6 was due to either an absence or downregulation of specific membrane structures or due to an overall downregulation of these adhesion mols. in all membrane structures in BCC. E-cadherin and CD44V6 were expressed in adherens junctions, desmosomes, and complex interdigitating membrane structures both in normal epidermis and in BCC. A quant. anal. showed that only a percentage of desmosomes was stained. In addn., the effect of pro-inflammatory cytokines, such as interferon-.gamma. (IFN-.gamma.) and tumor necrosis factor-.alpha. (TNF-.alpha.), was investigated in biopsy specimens of normal skin and BCC, using a biopsy culture system and immunohistochem. The expression of E-cadherin and CD44V6 was not significantly decreased after culturing BCC or normal skin biopsy specimens for 48 h with or without recombinant human (rHu)IFN-.gamma. or rHuTNF-.alpha.. It may be concluded that the decreased expression of both E-cadherin and CD44V6, obsd. in light microscopy, was not attributable to the absence of specific specialized structures in BCC and most likely also not caused by downregulation by local cytokines, but rather by generic downregulation of both of these adhesion mols. during malignant transformation.
REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L57 ANSWER 20 OF 42 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1999:668323 HCAPLUS
DOCUMENT NUMBER: 132:48340
TITLE: SHC-.alpha.5.beta.1 Integrin Interactions Regulate Breast Cancer **Cell Adhesion** and Motility
AUTHOR(S): Mauro, Loredana; Sisci, Diego; Bartucci, Monica; Salerno, Michele; Kim, Jerry; Tam, Timothy; Guvakova, Marina A.; Ando, Sebastiano; Surmacz, Eva
CORPORATE SOURCE: Kimmel Cancer Institute, Thomas Jefferson University, Philadelphia, PA, 19107, USA
SOURCE: Experimental Cell Research (1999), 252(2), 439-448
CODEN: ECREAL; ISSN: 0014-4827
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The oncogenic SHC proteins are signaling substrates for most receptor and cytoplasmic tyrosine kinases (TKs) and have been implicated in cellular growth, transformation, and differentiation. In tumor cells overexpressing TKs, the levels of tyrosine phosphorylated SHC are chronically elevated. The significance of amplified SHC signaling in

breast tumorigenesis and **metastasis** remains unknown. Here we demonstrate that seven- to ninefold overexpression of SHC significantly altered interactions of cells with fibronectin (FN). Specifically, in human breast cancer cells overexpressing SHC (MCF-7/SHC) the assocn. of SHC with .alpha.5.beta.1 integrin (FN receptor) was increased, spreading on FN was accelerated, and **basal** growth on FN was reduced. These effects coincided with an early decline of adhesion-dependent MAP kinase activity. **Basal** motility of MCF-7/SHC cells on FN was inhibited relative to that in several cell lines with normal SHC levels. However, when EGF or IGF-I was used as the chemoattractant, the locomotion of MCF-7/SHC cells was greatly (approx. fivefold) stimulated, while it was only minimally altered in the control cells. These data suggest that SHC is a mediator of the dynamic regulation of **cell adhesion** and motility on FN in breast cancer cells. (c) 1999 Academic Press.

REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L57 ANSWER 21 OF 42 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1999:644670 HCAPLUS
DOCUMENT NUMBER: 131:349771
TITLE: Tumor dormancy induced by downregulation of urokinase receptor in human carcinoma involves integrin and MAPK signaling
AUTHOR(S): Ghiso, Julio A. Aguirre; Kovalski, Katherine; Ossowski, Liliana
CORPORATE SOURCE: Rochelle Belfer Chemotherapy Foundation Laboratory, Division of Medical Oncology, Department of Medicine, Mount Sinai School of Medicine, New York, NY, 10029, USA
SOURCE: Journal of Cell Biology (1999), 147(1), 89-103
CODEN: JCLBA3; ISSN: 0021-9525
PUBLISHER: Rockefeller University Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Mechanisms that regulate the transition of **metastases** from clin. undetectable and dormant to progressively growing are the least understood aspects of cancer biol. Here, we show that a large (.apprx.70%) redn. in the urokinase plasminogen activator receptor (uPAR) level in human carcinoma HEp3 cells, while not affecting their in vitro growth, induced a protracted state of tumor dormancy in vivo, with G0/G1 arrest. We have now identified the mechanism responsible for the induction of dormancy. We found that uPA/uPAR proteins were phys. assocd. with .alpha.5.beta.1, and that in cells with low uPAR the frequency of this assocn. was significantly reduced, leading to a reduced avidity of .alpha.5.beta.1 and a lower **adhesion** of **cells** to the fibronectin (FN). Adhesion to FN resulted in a robust and persistent ERK1/2 activation and serum-independent growth stimulation of only uPAR-rich cells. Compared with uPAR-rich tumorigenic cells, the **basal** level of active extracellular regulated kinase (ERK) was four to sixfold reduced in uPAR-poor dormant cells and its stimulation by single chain uPA (scuPA) was weak and showed slow kinetics. The high **basal** level of active ERK in uPAR-rich cells could be strongly and rapidly stimulated by scuPA. Disruption of uPAR-.alpha.5.beta.1 complexes in uPAR-rich cells with antibodies or a peptide that disrupts uPAR-.beta.1 interactions, reduced the FN-dependent ERK1/2 activation. These results indicate that dormancy of low uPAR cells may be the consequence of insufficient uPA/uPAR/.alpha.5.beta.1 complexes, which cannot induce ERK1/2 activity

above a threshold needed to sustain tumor growth in vivo. In support of this conclusion we found that treatment of uPAR-rich cells, which maintain high ERK activity in vivo, with reagents interfering with the uPAR/.beta.1 signal to ERK activation, mimic the in vivo dormancy induced by downregulation of uPAR.

REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L57 ANSWER 22 OF 42 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1999:529341 HCAPLUS
DOCUMENT NUMBER: 131:155517
TITLE: Methods and reagents for the rapid and efficient isolation of circulating cancer cells using immunomagnetic enrichment combined with flow cytometric and immunocytochemical analysis
INVENTOR(S): Terstappen, Leon W. M. M.; Rao, Galla Chandra; Uhr, Jonathan W.; Racila, Emilian V.; Liberti, Paul A.
PATENT ASSIGNEE(S): Immunivest, USA; University of Texas Southwestern Medical Center/Dallas
SOURCE: PCT Int. Appl., 115 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9941613	A1	19990819	WO 1999-US3073	19990212
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2320418	AA	19990819	CA 1999-2320418	19990212
CA 2432361	AA	19990819	CA 1999-2432361	19990212
AU 9927636	A1	19990830	AU 1999-27636	19990212
AU 760560	B2	20030515		
BR 9907852	A	20001024	BR 1999-7852	19990212
EP 1062515	A1	20001227	EP 1999-908132	19990212
R: DE, FR, GB, IT, NL				
JP 2002503814	T2	20020205	JP 2000-531745	19990212
US 2003129676	A1	20030710	US 2002-269579	20021011

PRIORITY APPLN. INFO.:

US 1998-74535P	P	19980212
US 1998-110202P	P	19981130
US 1998-110279P	P	19981130
CA 1999-2320418	A3	19990212
US 1999-248388	A3	19990212
WO 1999-US3073	W	19990212
US 2001-904472	A1	20010713

AB A highly sensitive assay is disclosed which combines immunomagnetic enrichment with multiparameter flow cytometric and immunocytochem. anal. to detect, enumerate and characterize carcinoma cells in the blood. The

assay can detect one epithelial cell or less in 1 mL of blood and has a greater sensitivity than conventional PCR or immunohistochem. by 1-2 orders of magnitude. In addn., the assay facilitates the biol. characterization and staging of carcinoma cells. Levels of circulating epithelial cells were detd. in peripheral blood samples from breast, prostate, and colon cancer patients and in normal controls. Blood was treated with anti-epithelial **cell adhesion** mol. (EpCAM) monoclonal antibodies coupled to magnetic nanoparticles and magnetically sepd. The collected fraction was treated with FACS permeabilization soln., magnetically sepd., and treated with phycoerythrin conjugated anti-cytokeratin monoclonal antibody and peridinin chlorophyll protein-labeled CD45. Magnetically sepd. material was further treated with a nucleic acid dye. The samples were analyzed by FACS flow cytometry.

REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L57 ANSWER 23 OF 42 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1999:506056 HCAPLUS
DOCUMENT NUMBER: 132:48331
TITLE: Murine hepatic microvascular adhesion molecule expression is inducible and has a zonal distribution
AUTHOR(S): Wang, H. Helen; Nance, Dwight M.; Orr, F. William
CORPORATE SOURCE: Department of Pathology, Faculty of Medicine, University of Manitoba, Winnipeg, MB, R3E OW3, Can.
SOURCE: Clinical & Experimental Metastasis (1999), 17(2), 149-155
CODEN: CEXMD2; ISSN: 0262-0898
PUBLISHER: Kluwer Academic Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The structural and functional heterogeneity of hepatocytes and non-parenchymal cells across the liver lobule or acinus has been well documented. The geog. distribution and potential for induced expression of **adhesion** mols. on murine hepatic microvascular **cells** has not been reported, although these mols. are able to influence the metastatic outcome of intravascular cancer cells. We have postulated that the expression of **adhesion** mols. on these **cells** is susceptible to regulation by environmental factors and that these mols. have a zonal distribution across the acinus. To test this hypothesis, we injected C57BL/6 mice with bacterial lipopolysaccharide, 1 .mu.g/g body wt., i.p. At various time points (0-48 h) after stimulation, liver tissue sections were prepd. for immunohistochem. Confocal microscopy was used to detect the expression of vascular **cell adhesion** mol.-1 (VCAM-1), E-selectin, intercellular adhesion mol.-1 (ICAM-1) and .alpha.v integrin. The expression patterns were quant. measured by histomorphometry. Under **basal** conditions, ICAM-1 was weakly expressed in terminal portal veins while minimal VCAM-1 and no E-selectin were detected. Following stimulation with lipopolysaccharide, VCAM-1 and E-selectin were expressed on the endothelium of terminal portal veins and on sinusoidal lining cells with significantly stronger expression in the periportal zone than midzone. VCAM-1 expression peaked at 4 h and decreased gradually by 48 h. E-selectin peaked at 2 h and disappeared by 12 h after stimulation. ICAM-1 expression showed a much stronger and more uniform expression across the acinus with the peak reached by 4 h and sustained for longer than 48 h after lipopolysaccharide administration. The .alpha.v integrin was not detected under **basal** conditions or

after lipopolysaccharide stimulation. Expression of all these adhesion mols. (ICAM-1, VCAM-1, E-selectin and .alpha.v integrin) was induced by growth of B16F1 melanoma cells in the peritoneal cavity of the mouse. These results support the hypotheses that expression of microvascular adhesion mols. in the mouse liver is susceptible to regulation by environmental stimuli and has a zonal heterogeneity across the acinus.
REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L57 ANSWER 24 OF 42 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1999:374850 HCAPLUS
DOCUMENT NUMBER: 131:156375
TITLE: R-Ras signals through specific integrin .alpha. cytoplasmic domains to promote migration and invasion of breast epithelial cells
AUTHOR(S): Keely, Patricia J.; Rusyn, Elena V.; Cox, Adrienne D.; Parise, Leslie V.
CORPORATE SOURCE: Department of Pharmacology, University of North Carolina, Chapel Hill, NC, 27599, USA
SOURCE: Journal of Cell Biology (1999), 145(5), 1077-1088
CODEN: JCLBA3; ISSN: 0021-9525
PUBLISHER: Rockefeller University Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Specificity and modulation of integrin function have important consequences for cellular responses to the extracellular matrix, including differentiation and transformation. The Ras-related GTPase, R-Ras, modulates integrin affinity, but little is known of the signaling pathways and biol. functions downstream of R-Ras. Here we show that stable expression of activated R-Ras or the closely related TC21 (R-Ras 2) induced integrin-mediated migration and invasion of breast epithelial cells through collagen and disrupted differentiation into tubule structures, whereas dominant neg. R-Ras had opposite effects. These results imply novel roles for R-Ras and TC21 in promoting a transformed phenotype and in the **basal** migration and polarization of these cells. Importantly, R-Ras induced an increase in **cellular adhesion** and migration on collagen but not fibronectin, suggesting that R-Ras signals to specific integrins. This was further supported by expts. in which R-Ras enhanced the migration of cells expressing integrin chimeras contg. the .alpha.2, but not the .alpha.5, cytoplasmic domain. In addn., a transdominant inhibition previously noted only between integrin .beta. cytoplasmic domains was obsd. for the .alpha.2 cytoplasmic domain; .alpha.2.beta.1-mediated migration was inhibited by the expression of excess .alpha.2 but not .alpha.5 cytoplasmic domain-contg. chimeras, suggesting the existence of limiting factors that bind the integrin .alpha. subunit. Using pharmacol. inhibitors, we found that R-Ras induced migration on collagen through a combination of phosphatidylinositol 3-kinase and protein kinase C, but not MAPK, which is distinct from the other Ras family members, Rac, Cdc42, and N- and K-Ras. Thus, R-Ras communicates with specific integrin .alpha. cytoplasmic domains through a unique combination of signaling pathways to promote cell migration and invasion.
REFERENCE COUNT: 85 THERE ARE 85 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L57 ANSWER 25 OF 42 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1999:512 HCAPLUS

DOCUMENT NUMBER: 130:178176
TITLE: Cloning and characterization of the human .beta.4-integrin gene promoter and enhancers
AUTHOR(S): Takaoka, Asako Suzuki; Yamada, Tesshi; Gotoh, Masahiro; Kanai, Yae; Imai, Kohzoh; Hirohashi, Etsuo
CORPORATE SOURCE: Pathology Division, National Cancer Center Research Institute, Chuo-ku, Tokyo, 104-0045, Japan
SOURCE: Journal of Biological Chemistry (1998), 273(50), 33848-33855
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The **cell**-surface **adhesion** mol. .alpha.6.beta.4-integrin is a receptor for laminins and a component of hemidesmosomes. .beta.4-Integrin expression is restricted to proliferating **basal** keratinocytes in the epidermis and is suppressed when differentiation commences. Altered .beta.4-integrin expression levels correlate significantly with the aggressive behavior of cancers. In order to clarify the mechanisms that regulate transcription of the .beta.4-integrin gene, the authors cloned its 5'-flanking region. This 5'-flanking region was found to have a high G + C content and not to contain either TATA or CAAT boxes. Nested delimitation and reporter analyses mapped a **basal** promoter to nucleotides -106 to +105, surrounding the most proximal transcription initiation site. Gel retardation and mutational analyses revealed that cooperation between AP1 and Ets, interacting with other factors, mediated the promoter activity. In addn. to the promoter element, enhancer activity was found in the first intron (+1905/+3933) and in a sequence upstream of the promoter region (-414/-107). These findings should facilitate the understanding of the regulation of .beta.4-integrin gene expression in processes such as cell growth and differentiation, apoptosis, and cancer development and **metastasis**.
REFERENCE COUNT: 72 THERE ARE 72 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L57 ANSWER 26 OF 42 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1998:161916 HCAPLUS
DOCUMENT NUMBER: 128:266494
TITLE: Melatonin reduces the invasive capacity of MCF-7 human breast cancer cells. In vitro studies
AUTHOR(S): Cos, S.; Sanchez-Barcelo, E. J.
CORPORATE SOURCE: Department Physiology Pharmacology, School Medicine, University Cantabria, Santander, 39011, Spain
SOURCE: Pineal Update: From Molecular Mechanisms to Clinical Implications, [Colloquium of the European Pineal Society], 7th, Sitges, Spain, Mar. 29-31, 1996 (1997), Meeting Date 1996, 377-382. Editor(s): Webb, Susan M. PJD Publications: Westbury, N. Y.
CODEN: 65TBA5
DOCUMENT TYPE: Conference
LANGUAGE: English
AB Melatonin (MEL) has a direct oncostatic effect on estradiol (E2) responsive MCF-7 cells in culture. The purpose of the present study was to investigate whether MEL reduces the metastatic behavior of MCF-7 cells. MEL (1 nM) reduced the **basal** invasion of MCF-7 cells, as well as E2-induced invasion. Sub (0.1 pM) or supra-physiol. (10 .mu.M) concns. of

MEL lacked this effect. The pretreatment of MCF-7 cells with 1 nM MEL increased the response of tumor cells to the anti-invasive effects of this indoleamine. To explore the mechanisms involved in the anti-invasive effects of MEL, the authors measured its influence on these processes: the attachment of MCF-7 cells to a basement membrane, the chemotactic response of the cells, and, the type IV collagenolytic activity. The authors have concluded that: the presence of MEL (1 nM) in the culture media significantly reduces the ability of MCF-7 cells to attach to the basement membrane; this effect is enhanced by pretreating the cells with the same indolamine. MEL also counteracts the stimulatory effects of E2 on **cell adhesion**. MEL (1 nM) decreases the chemotactic response of MCF-7 cells to fibronectin. MEL does not influence the type IV collagenolytic activity of MCF-7 cells. These results suggest that MEL not only reduces the proliferation of MCF-7 cells in vitro, but also their invasiveness, causing a decrease in cell attachment and cell motility, probably by interacting with the E2-mediated mechanisms of MCF-7 cell invasiveness.

REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L57 ANSWER 27 OF 42 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1997:726325 HCAPLUS
DOCUMENT NUMBER: 128:12240
TITLE: Hydrogen peroxide production by interleukin-1 (IL-1)-activated hepatic sinusoidal endothelium contributes to liver **metastasis** progression
AUTHOR(S): Anadgasti, M. J.; Alvarez, A.; Martin, J. J.; Mendoza, L.; Vidal-Vanachocha, F.
CORPORATE SOURCE: Dep. Cellular Biol. & Morphological Scis., Univ. Basque Country Sch. Med. Dentistry, Vizcaya, 48940, Spain
SOURCE: Cells of the Hepatic Sinusoid (1997), Volume Date 1996, 6, 402-406
CODEN: CHSIEL
PUBLISHER: Kupffer Cell Foundation
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Endotoxins, interleukin-1 (IL-1) and other pro-inflammatory mediators have been shown to promote hepatic **metastasis**. The authors have investigated the involvement of ROS released by IL-1 stimulated HSE in this promoting effect. Recombinant human IL-1.beta. (rHuIL.beta.) (5 .mu.g/kg) was i.v. injected and the hepatic **metastasizing** ability of B16 melanoma cells following intrasplenic injection was studied in the presence of ROS scavengers. RHuIL-1.beta.-promoted hepatic **metastases** were significantly reduced by catalase (1 mg/kg) and enhanced by SOD (5 mg/kg), rHuIL-1.beta.- stimulated HSE-conditioned medium (HSE-CM) significantly enhanced B16 melanoma **cell adhesion** to HSE compared to unstimulated HSE-CM, which in turn also significantly increased melanoma cell adherence compared to **basal** medium. Addn. of catalase completely abrogated pro-adhesive effects induced by rHuIL-1.beta.-stimulated HSE-CM with respect to unstimulated HSE-CM, but did not affect the pro-adhesive effects induced by unstimulated HSE- CM over **basal** medium. The invasive capacity of melanoma cells through reconstituted basement membrane matrigel was significantly enhanced in the presence of HSE-CM compared to controls receiving **basal** medium. Catalase 50% reduced these pro-invasive effects. Melanoma cell damaged was obsd. from the 2nd hour

of adhesion to HSE and significantly increased when the cells adhered to rHuIL-1.beta.-stimulated HSE. This increased was abrogated by catalase. Cytolysis of the HSE was not obsd. during melanoma **cell adhesion**. Neither was the enhancement of B16 melanoma hydrogen peroxide prodn. obsd. in response to rHuIL-1.beta.. Thus, the effects of IL-1 in the liver may consist of a balance between the pro-metastatic effect of enhanced adherence to the HSE and the antimetastatic effect of hydrogen peroxide-mediated cytotoxicity. The results suggest that the enhancement of hydrogen peroxide prodn. by the rHuIL-1.beta.-stimulated HSE may contribute to the hepatic **metastasis** progression of ROS-resistant melanoma cells. Results in vitro indicate that this progression is assocd. with a hydrogen peroxide-mediated increase in melanoma **cell adhesion** to HSE and chemoinvasion through connective tissue matrix.

REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L57 ANSWER 28 OF 42 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1997:431513 HCAPLUS
DOCUMENT NUMBER: 127:160152
TITLE: Effect of cytokines on tumor cell-endothelial interactions
AUTHOR(S): Cohen, Marion C.; Bereta, Michal; Bereta, Joanna
CORPORATE SOURCE: Department of Pathology and Laboratory Medicine, UMDNJ-NJ Medical School, Newark, NJ, 07103, USA
SOURCE: Indian Journal of Biochemistry & Biophysics (1997), 34(1&2), 199-204
CODEN: IJBBBQ; ISSN: 0301-1208
PUBLISHER: National Institute of Science Communication
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review and discussion with 59 refs. The adherence of tumor cells to microvascular endothelium is believed to be a necessary step in their migration to sites of **metastasis**. This process occurs when cell surface mols. on tumor cells bind to complementary sites on endothelial cells. The expression of these endothelial adhesion mols. appears to be modulated by cytokines. Exposure of endothelium to some cytokines augments the **adhesion** of inflammatory **cells** as well as tumor cells in in vitro assays. In a murine model consisting of P815 mastocytoma cells and microvascular endothelium it was found that pretreatment of endothelial monolayers with TNF-.alpha., IL-1, LPS, or PMA augmented the no. of tumor cells that attach in a dose-dependent fashion. The change in binding was due to an increase in the expression of VCAM-1 on the endothelium surface. Methylxanthines as well as "classical" calcium-mobilizing agents inhibited the expression of VCAM-1 in MME. The possible mechanisms of TNF-.alpha. signal transduction in endothelial cells was also studied. Studies suggest that the "classical" PKC pathway is not completely responsible for signaling since TNF-.alpha. did not cause translocation of PKC to the cell membrane and its effect could not be completely mimicked by PMA. The authors also studied the effect of TGF-.beta. on the binding of tumor cells to endothelium. TGF-.beta.-mediated inhibition of both **basal** binding and TNF-.alpha.-enhanced P815 binding to endothelium is completely abolished in the presence of the protein phosphatase inhibitor okadaic acid suggesting that TGF-.beta. elicits its effect by stimulating protein phosphatase activity.

L57 ANSWER 29 OF 42 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1997:394397 HCAPLUS
DOCUMENT NUMBER: 127:93477
TITLE: Liver endothelial E-selectin mediates carcinoma **cell adhesion** and promotes liver **metastasis**
AUTHOR(S): Brodt, P.; Fallavollita, L.; Bresalier, R. S.; Meterissian, S.; Norton, C. R.; Wolitzky, B. A.
CORPORATE SOURCE: Department of Surgery and Oncology, Division of Surgical Research, McGill University, Montreal, QC, Can.
SOURCE: International Journal of Cancer (1997), 71(4), 612-619
CODEN: IJCNAW; ISSN: 0020-7136
PUBLISHER: Wiley-Liss
DOCUMENT TYPE: Journal
LANGUAGE: English
AB E-selectin is a cytokine-inducible endothelial **cell adhesion** receptor which is involved in the process of leukocyte rolling, the first in a cascade of interactions leading to leukocyte transmigration. Several studies have implicated this receptor in carcinoma **cell adhesion** to the endothelium, an interaction thought to be required for tumor extravasation during **metastasis**. To study the role of this receptor in the process of **metastasis**, the authors utilized a murine carcinoma line H-59 which is highly metastatic to the liver in vivo. When **adhesion** of H-59 **cells** to primary cultures of murine hepatic endothelial cells was measured, it was found that the tumor cells had a low **basal** level of **adhesion** to the sinusoidal endothelial **cells**, which could be significantly and specifically augmented by pre-activation of the endothelial cells with rTNF.alpha.. This incremental increase in adhesion to the activated endothelium could be completely and specifically abolished by a neutralizing monoclonal antibody to murine E-selectin (MAb 9A9). Similar results were obtained with 2 highly metastatic human colorectal carcinoma lines, HM 7 and CX-1, but not with a second murine subline, M-27, which is poorly metastatic to the liver. To assess the role of E-selectin in **metastasis** to the liver in vivo, the effect of MAb 9A9 on exptl. liver **metastasis** was evaluated using the syngeneic H-59 model. The authors show here that this antibody caused a marked specific and Fc-independent inhibition of exptl. liver **metastasis**, reducing the median no. of **metastases** by 97% relative to the control groups. The authors' results provide evidence that endothelial E-selectin is a mediator of carcinoma **metastasis** to the liver.

L57 ANSWER 30 OF 42 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1997:282668 HCAPLUS
DOCUMENT NUMBER: 126:325021
TITLE: Influence of bacterial polysaccharides on **adhesive** properties of 3LL carcinoma **cells** in model of metastatic process in vitro
AUTHOR(S): Shmalko, Yu. P.; Varbanets, L. D.; Chaly, A. P.; Pliss, A. P.
CORPORATE SOURCE: R.E. Kavetsky Institute of Experimental Pathology, Oncology and Radiobiology, National Academy of Sciences of Ukraine, Kiev, 252022, Ukraine
SOURCE: Eksperimental'naya Onkologiya (1996), 18(4), 423-425
CODEN: EKSODD; ISSN: 0204-3564

PUBLISHER: Institut Eksperimental'noi Patologii, Onkologii i Radiobiologii im. R. E. Kavetskogo NAN Ukrainy
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In model system in vitro using fibroblasts NIH3T3 and **basal** membrane components produced by them the influence of bacterial polysaccharides (PS) and lipopolysaccharides (LPS) isolated from Clavibacter michiganense and Pseudomonas solanacearum on **adhesive** properties of 3LL carcinoma **cells** has been studied. PS and LPS bound to receptors of tumor cells (TC) and blocked the ability of the latter to interact with receptors of **basal** membrane of fibroblasts. This phenomenon is apparently the basis of the redn. of TC adhesion under the influence of PS and LPS.

L57 ANSWER 31 OF 42 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1997:273064 HCAPLUS
DOCUMENT NUMBER: 126:315695
TITLE: Sinusoidal endothelium release of hydrogen peroxide enhances very late antigen-4-mediated melanoma cell adherence and tumor cytotoxicity during interleukin-1 promotion of hepatic melanoma **metastasis** in mice
AUTHOR(S): Anasagasti, Miren J.; Alvarez, Antonia; Martin, Javier J.; Mendoza, Lorea; Vidal-Vanaclocha, Fernando
CORPORATE SOURCE: Department of Cell Biology and Morphological Sciences, School of Medicine and Dentistry, University of the Basque Country, Leioa, Spain
SOURCE: Hepatology (Philadelphia) (1997), 25(4), 840-846
CODEN: HPTLD9; ISSN: 0270-9139
PUBLISHER: Saunders
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The hepatic sinusoidal endothelium (HSE) releases large amts. of reactive oxygen species (ROS) in response to endotoxins and interleukin-1 (IL-1). Such proinflammatory mediators have been shown to promote hepatic **metastasis**. The authors have investigated the involvement of ROS released by IL-1-stimulated HSE in this promoting effect. Recombinant human interleukin-1.beta. (rHuIL-1.beta.) (5 .mu.g/kg) was i.v. injected into C57BL/6J mice, and the hepatic **metastasizing** ability of B16 melanoma cells following intrasplenic injection was studied in the presence of ROS scavengers. RHuIL-1.beta.-promoted hepatic **metastases** were significantly reduced by catalase (1 mg/kg) and enhanced by recombinant human superoxide dismutase (rHuSOD) (5 mg/kg). RHuIL-1.beta.-stimulated HSE-conditioned medium (HSE-CM) significantly enhanced B16 melanoma **cell adhesion** to HSE compared with unstimulated HSE-CM, which in turn also significantly increased with melanoma cell adherence compared with **basal** medium. The addn. of catalase completely abrogated proadhesive effects induced by rHuIL-1.beta.-stimulated HSE-CM with respect to unstimulated HSE-CM, but did not affect the proadhesive effects induced by unstimulated HSE-CM over **basal** medium. The rat monoclonal antibody to mouse vascular **cell adhesion** mol.-1 (VCAM-1) significantly inhibited the enhanced melanoma cell adherence effects of both unstimulated and rHuIL-1.beta.-stimulated HSE-CM, indicating that adherence was very late antigen-4 (VLA-4)-mediated. Not surprisingly, the percentage of VLA-4 expressing B16 melanoma cells significantly increased in response to unstimulated (21% of controls) and rHuIL-1.beta.-stimulated (32% of

controls) HSE-CM. Catalase addn. abrogated these effects of rHuIL-1.beta.-stimulated-HSE-CM. Melanoma cell damage was obsd. from the second hour of adhesion to HSE and significantly increased when the cells adhered to rHuIL-1.beta.-stimulated HSE. This increase was abrogated by catalase. Cytolysis of the HSE was not obsd. during melanoma **cell adhesion**. Neither was the enhancement of B16 melanoma hydrogen peroxide prodn. obsd. in response to rHuIL-1.beta.. Thus, the effects of IL-1 in the liver may consist of a balance between the prometastatic effect of enhanced adherence to the HSE and the antimetastatic effect of H2O2-mediated cytotoxicity. The results suggest that the enhancement of H2O2 prodn. by the rHuIL-1.beta.-stimulated HSE may contribute to the hepatic **metastasis** progression of ROS-resistant melanoma cells. Results in vitro indicate that this progression is assocd. with a H2O2-mediated increase in melanoma **cell adhesion** to HSE.

L57 ANSWER 32 OF 42 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1997:269623 HCAPLUS
DOCUMENT NUMBER: 126:328881
TITLE: Clinical significance of .alpha.v.beta.3 integrin and intercellular adhesion molecule-1 expression in cutaneous malignant melanoma lesions
AUTHOR(S): Natali, Pier Giorgio; Hamby, Carl V.; Felding-Habermann, Brunhilde; Liang, Bitao; Nicotra, Maria R.; Di Filippo, Franco; Giannarelli, Diana; Temponi, Massimo; Ferrone, Soldano
CORPORATE SOURCE: Department of Immunology, Regina Elena Cancer Institute, Rome, 00158, Italy
SOURCE: Cancer Research (1997), 57(8), 1554-1560
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Several lines of exptl. evidence in in vitro and animal model systems suggest that the integrin .alpha.v.beta.3 plays a role in the tumorigenicity of human melanoma cells and that the blocking of .alpha.v.beta.3 ligand binding can inhibit tumor progression. However, there is only scanty information about the role of .alpha.v.beta.3 in malignant melanoma in a clin. setting. Therefore, in the present study, the authors have analyzed the distribution in lesions of melanocyte origin and in normal tissues of the .alpha.v integrin subunit and of the .alpha.v.beta.3 complex and their assocn. with histopathol. and clin. parameters of malignant melanoma. The authors have used as probes the monoclonal antibodies (mAbs) TP36.1 and VF27.263.15, which are specific for the .alpha.v subunit and for the .alpha.v.beta.3 complex, resp. In immunohistochem. assays, mAb TP36.1 stained both benign and malignant lesions of melanocyte origin. In contrast, the reactivity of mAb VF27.263.15 was restricted to malignant lesions. Both mAbs displayed differential reactivity with primary melanoma lesions of different histotypes because they stained about 50% of acral lentiginous melanoma and superficial spreading melanoma lesions, at least 80% of nodular melanoma lesions, and none of the uveal melanoma lesions tested. Both mAbs TP36.1 and VF27.263.15 stained about 60% of lymph node **metastases** and 80% of cutaneous **metastases**. Expression of the .alpha.v.beta.3 complex in melanocytic lesions resembles that of intercellular adhesion mol.-1 (ICAM-1) in several respects: (a) both are expressed in a significantly larger proportion of malignant than of benign

lesions; (b) expression of both mols. in primary melanoma lesions is significantly assocd. with lesion thickness; and (c) expression of both mols. in primary lesions from patients with stage I melanoma is significantly assocd. with an increased probability of disease recurrence following surgical excision. .alpha.v.beta.3 And ICAM-1 in primary melanoma lesions complement each other in predicting the outcome of the disease, because the assocn. with prognosis was enhanced when primary lesions were stained by both anti-.alpha.v.beta.3 mAb VF27.263.15 and anti-ICAM-1 mAb CL203.4 or by neither mAb. Because .alpha.v.beta.3 has been suggested as a potential target of immunotherapy, its distribution in normal tissues was investigated. .alpha.v.beta.3 Expression is restricted because it was only detected in ductal epithelium of parotid glands, thyrocytes, **basal** glands of the stomach, colonic and rectal epithelium, glomeruli, Bowman's capsules, proximal and distal tubules of the kidneys, and endometrial epithelium. These findings suggest that renal function will be a crit. clin. parameter to monitor in therapies of malignant diseases relying on systemic administration of anti-.alpha.v.beta.3 mAb.

L57 ANSWER 33 OF 42 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1997:37437 HCAPLUS
DOCUMENT NUMBER: 126:58230
TITLE: CD44: prognostic relevance in different skin tumors
AUTHOR(S): Seiter, Simone; Schadendorf, Dirk; Tilgen, Wolfgang; Zoeller, Margot
CORPORATE SOURCE: Department of Dermatology, University of Heidelberg, Heidelberg, 69115, Germany
SOURCE: International Congress Series (1996), 1114(Head and Neck Cancer: Advances in Basic Research), 651-657
CODEN: EXMDA4; ISSN: 0531-5131
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Splice variants of CD44 (CD44v) are important for the lymphatic spread of rat carcinoma cells. In several human tumors, too, expression of CD44v correlates with tumor progression. However, little is known about the physiol. functions of distinct variant exons. Here the authors report on the immunohistol. evaluation of CD44v expression in **basal** cell carcinomas (BCC), squamous cell carcinomas (SCC), nevi, primary melanoma, cutaneous and lymph node **metastases** using antibodies recognizing epitopes of the CD44 std. isoform and variant exons v5, v6, v7, v7-v8, and v10. Compared to the expression on human skin, CD44v expression, particularly CD44v10, was downregulated in BCCs and SCCs. Melanocytes did not express any variant exons; nevi as well as primary melanomas and melanoma **metastases** stained to a varying degree with anti-CD44v5, anti-CD44v7-v8, and anti-CD44v10. Exons v6 and v7 were not detected on any of these tissues. Expression of exon v10 was upregulated in thick primary tumors and skin **metastases**; lymph node **metastases** displayed elevated levels of exon v5. Since benign as well as malignant growth was accompanied by expression of CD44 variant isoforms, a linkage between expression of CD44 variant isoforms and malignant transformation or tumor progression was excluded, the distinct expression patterns of CD44v5 and v10 in skin and lymph node **metastasis** point towards the functional importance of these exons in melanoma progression. The data suggest that distinct isoforms have defined functions. Exons v5 and v6 seem to be involved in signal transduction and proliferation; exon v10 appears to be required for

maintaining epidermal structures and homing into the skin.

L57 ANSWER 34 OF 42 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1996:493640 HCAPLUS
DOCUMENT NUMBER: 125:159451
TITLE: Epidermal growth factor modulates cell attachment to hyaluronic acid by the cell surface glycoprotein CD44
AUTHOR(S): Zhang, Ming; Singh, Raj K.; Wang, Ming Hui; Wells, Alan; Siegal, Gene P.
CORPORATE SOURCE: Department Pathology, University Alabama, Birmingham, AL, 35233, USA
SOURCE: Clinical & Experimental Metastasis (1996), 14(3), 268-276
CODEN: CEXMD2; ISSN: 0262-0898
PUBLISHER: Rapid Science Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English
AB **Cell adhesion** to and migration through extracellular matrixes (ECM) are crit. events in tumor invasion and **metastasis**. Previous work by us had demonstrated that signaling of epidermal growth factor receptor (EGFR) confers an oncogenic phenotype on NR6 cells and that these cells when transfected with holo EGFR demonstrate greater motility and invasiveness than cells carrying a carboxy-terminal truncated EGFR. Recently, a cell surface glycoprotein, CD44, has been implicated in **cell**-ECM **adhesion** involved in tumor **cell** migration, signal transduction, and **metastasis**. We investigated whether EGF regulates cellular interactions with ECM components, and in particular, hyaluronate, by modulating CD44 expression. In vitro cell attachment assays on hyaluronate-coated plates demonstrated similar **basal** level of binding (.apprx. 33%) for murine NR6 parental cells devoid of endogenous EGFR (P) or expressing wild-type EGFR (WT), while a time-dependent increase in binding was obsd. in WT cells stimulated with EGF. Addnl., utilizing monoclonal antibody blocking assays, CD44, but not EGFR, was shown to be directly involved in this attachment. Both WT and P cells possessed equiv. 95 kDa bands on immunoblots, corresponding to CD44. The existence of CD44 mRNA was verified by RT-PCR using synthetic oligonucleotides in which a 1.1 kb cDNA was detected in both cell lines and confirmed by DNA sequencing. After 24-h exposure to exogenous EGF, an increase in CD44 protein and mRNA expression was found in WT cells, but not in P cells, supporting the contention that a functional EGFR signaling pathway is required for CD44 regulation. Thus, EGF stimulates cell binding to hyaluronate in vitro by regulating CD44 expression.

L57 ANSWER 35 OF 42 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1996:455520 HCAPLUS
DOCUMENT NUMBER: 125:218485
TITLE: Immunohistochemical study on expression of focal adhesion protein and pattern of **basal** membrane in human oral squamous cell carcinoma
AUTHOR(S): Terakado, Nagaaki
CORPORATE SOURCE: Dent. Sch., Okayama Univ., Okayama, 700, Japan
SOURCE: Okayama Shigakkai Zasshi (1996), 15(1), 63-72
CODEN: OSZAE3; ISSN: 0913-3941
PUBLISHER: Okayama Shigakkai
DOCUMENT TYPE: Journal
LANGUAGE: Japanese
AB P125 focal adhesion kinase (FAK) and paxillin should play important role

in signal transduction of the invasion and **metastasis** of oral squamous cell carcinoma, and type IV collagen and laminin bore the defending role. Paxillin and vinculin were pos. in 28/49 and 2/49, resp. The pos. rate was higher in advanced stage of Grade 4 ($p < 0.01$), and the cases with **metastasis** ($p < 0.05$). FAK was pos. in 29/49, and 24/49 was pos. for both paxillin and FAK. Basement membrane was damaged in the cases with **metastasis**. The conditions of the basement exhibited no correlation with the expression of FAK. Paxillin or vinculin might be useful for the marker of the metastatic activity of oral squamous cell carcinoma.

L57 ANSWER 36 OF 42 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1996:398300 HCAPLUS
DOCUMENT NUMBER: 125:55072
TITLE: The role of calcium in the regulation of invasion and angiogenesis
AUTHOR(S): Alessandro, Riccardo; Masiero, Laura; Liotta, Lance A.; Kohn, Elise C.
CORPORATE SOURCE: Laboratory Pathology, National Cancer Institute, Bethesda, MD, USA
SOURCE: In Vivo (1996), 10(2), 153-160
CODEN: IVIVE4; ISSN: 0258-851X
PUBLISHER: International Institute of Anticancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The complex process of invasion and **metastasis** is now being dissected at the level of cell-cell and cell-substratum signaling. Tools for doing so include mechanisms for the investigation of cellular actions, such as the identification of agents that can be used to examine the signaling pathways involved in adhesion, proteolysis, motility, and angiogenesis. The authors have demonstrated that CAI, carboxyamido-triazole, selectively inhibits calcium uptake, stimulated or **basal**, and thereby modulates the elements involved in invasion and angiogenesis. Through modulation of cellular calcium balance, CAI secondarily inhibits calcium-dependent signaling pathways, such as release of second messengers, protein phosphorylation and gene transcription. The authors have demonstrated that CAI treatment resulted in inhibition of endothelial **cell adhesion**, migration, expression of proteolytic enzymes, and vessel formation in vitro and in vivo. The process of endothelial **cell adhesion** and spreading on extracellular matrix substrata results in an increase in intracellular calcium that can be inhibited by CAI exposure. Furthermore, endothelial **cell adhesion** and spreading on type IV collagen stimulates the secondary signaling events of tyrosine phosphorylation of focal adhesion kinase (pp125FAK) and autophosphorylation of pp125FAK. CAI treatment of the endothelial cells inhibited cell spreading, and both the induction of pp125FAK phosphorylation and the phosphorylation of exogenous substrates by pp125FAK kinase. These data indicate that regulation of cellular events key in the process of angiogenesis may be modulated by intracellular calcium balance thereby creating a new therapeutic target for anticancer research. CAI is in phase I clin. trial for patients with advanced cancers, yielding plasma concns. in the in vitro anti-angiogenic range.

L57 ANSWER 37 OF 42 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1995:851645 HCAPLUS
DOCUMENT NUMBER: 124:166052

TITLE: Transforming growth factor .beta.1 inhibits invasion of differentiated thyroid carcinoma via modulation of tumor **cell adhesion** and motility
AUTHOR(S): Hoelting, T.; Duh, O. A.; Clark, O. H.; Herfarth, C.
CORPORATE SOURCE: Chirurgische Klin., Univ. Heidelberg, Heidelberg, D-69120, Germany
SOURCE: Chirurgisches Forum fuer Experimentelle und Klinische Forschung (1995) 299-302
CODEN: CFEKA7; ISSN: 0303-6227
PUBLISHER: Springer
DOCUMENT TYPE: Journal
LANGUAGE: German
AB Transforming growth factor .beta.1 (TGF .beta.1) inhibits invasion of follicular (FTC) thyroid cancer cells. The authors investigated whether TGF .beta.1 affects motility and **adhesion** in 3 FTC **cell** lines from 1 patient (FTC133-primary; FTC236-lymph node- and FTC238-lung **metastasis**). Using the MTT-assay, the effect of TGF .beta.1 on attachment of tumor cells to major components of the extracellular matrix (ECM) and on penetration of 8 .mu.m pore polycarbonate membranes vs. ECM was studied. Collagen IV increased adhesion of FTC133 by 48% and fibronectin by 30%. Laminin, collagen I and Matrigel did not significantly affect adhesion. TGF .beta.1 (10 ng/mL) increased **basal** adhesion of FTC133 by 14%, to collagen IV by another 21% and to fibronectin by 17%. Collagen IV and fibronectin also stimulated tumor cell motility; 28% more FTC133 had migrated towards collagen IV (fibronectin: 22%). TGF .beta.1 reduces invasion and protease activity of follicular and papillary thyroid cancer cells. The present study suggests that this effect is achieved by a possible regulation of tumor **cell** motility and **adhesion**.

L57 ANSWER 38 OF 42 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1995:286447 HCAPLUS
DOCUMENT NUMBER: 122:52958
TITLE: Characterization of integrin expression and regulation on SW-480 human colon adenocarcinoma cells and the effect of rhodostomin on **basal** and upregulated tumor **cell adhesion**
AUTHOR(S): Chiang, Huei-Shien; Peng, Hui-Chin; Huang, Tur-Fu
CORPORATE SOURCE: Pharmacological Institute, College of Medicine, National Taiwan University, No. 1, Sec. 1, Jen-Ai Rd., Taipei, Taiwan
SOURCE: Biochimica et Biophysica Acta (1994), 1224(3), 506-16
CODEN: BBACAQ; ISSN: 0006-3002
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Integrins are a superfamily of cell surface glycoproteins that mediate cell-extracellular matrix (ECM) and **cell-cell adhesion**. Immunofluorescence microscopy and flow cytometric anal. using anti-integrin mAbs as the primary binding ligands demonstrated that the platelet integrin receptor .alpha.IIb.beta.3, as well as .alpha.v.beta.3, .alpha.5.beta.1 and .alpha.6.beta.1, are present on the surface of SW-480 human colon adenocarcinoma cells. Monoclonal antibodies (mAbs) against .alpha.IIb.beta.3 and .alpha.5.beta.1 inhibited unstimulated **basal** adhesion to fibronectin by approx. 30% and 40%, resp. The surface immunoreactivity of tumor cells for .alpha.IIb.beta.3 was enhanced by pretreatment (5 min) with a phorbol

ester (12-O-tetradecanoylphorbol-13-acetate (TPA)) or a lipoxygenase metabolite of arachidonic acid, 12-hydroxyeicosatetraenoic acid (12-HETE) in a dose- and time-dependent manner. SW-480 cells possess a large intracellular pool of .alpha.IIb.beta.3, from which the receptor complex translocates to the cell surface following pretreatment with TPA or 12(S)-HETE. This pretreatment enhances adhesion to fibronectin, which is mediated exclusively by .alpha.IIb.beta.3 integrins. Staurosporine was found to block .alpha.IIb.beta.3 up-regulation and enhanced-adhesion. TPA and 12(S)-HETE also facilitated the redistribution of .alpha.IIb.beta.3 during the enhanced-spreading process. Rhodostomin, an Arg-Gly-Asp- (RGD) contg. antiplatelet snake venom peptide, was about 400-times more potent than RGDS at inhibiting control, TPA- or 12(S)-HETE-enhanced **adhesion** of SW-480 **cells** to fibronectin. The binding of mAbs against .alpha.IIb.beta.3, .alpha.v.beta.3 and .alpha.5.beta.1 was inhibited by pretreatment with rhodostomin, suggesting that rhodostomin binds via its RGD sequence to multiple integrin receptors (i.e., .alpha.IIb.beta.3, .alpha.v.beta.3, .alpha.5.beta.1) expressed on the SW-480 **cell** surface, inhibiting **cell adhesion** to ECM.

L57 ANSWER 39 OF 42 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1994:627575 HCAPLUS
DOCUMENT NUMBER: 121:227575
TITLE: Transforming growth factor-.beta.1 is a negative regulator for differentiated thyroid cancer: studies of growth, migration, invasion, and adhesion of cultured follicular and papillary thyroid cancer cell lines
AUTHOR(S): Hoelting, Thomas; Zielke, Andreas; Siperstein, Allan E.; Clark, Orlo H.; Duh, Quan-Yang
CORPORATE SOURCE: Dep. Surg., Univ. Heidelberg, Heidelberg, Germany
SOURCE: Journal of Clinical Endocrinology and Metabolism (1994), 79(3), 806-13
CODEN: JCEMAZ; ISSN: 0021-972X
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Invasion and **metastasis** may be caused by the escape of tumor cells from the neg. control of growth factors. The authors analyzed the effects of transforming growth factor-.beta.1 (TGF.beta.1) on growth, migration, invasion, and **adhesion** in three follicular thyroid cancer **cell** lines (FTC133, primary; FTC236, lymph node **metastasis**; FTC238, lung **metastasis**) from one patient and in a papillary line (PTC-UC3). Cell growth was measured by dimethylthiazol-diphenyltetrazolium bromide assays, and migration (**basal** or epidermal growth factor stimulated) was detd. by the ability of cells to penetrate 8-.mu.m pore membranes that were covered with Matrigel for invasion assays. Moreover, the authors studied tumor **cell adhesion** to collagen type IV, fibronectin, and laminin. TGF.beta.1 inhibited growth in FTC (FTC133, by 31%; FTC236, 15%; FTC238, 17%), but not in PTC. Migration was inhibited in all cell lines. TGF.beta.1 inhibited epidermal growth factor-stimulated migration of FTC133 by 43% vs. 29% without epidermal growth factor. TGF.beta.1 also inhibited invasion (FTC133, 32%; FTC236, 18%; FTC238, 15%; PTC-UC3, 32%). All cell lines adhered preferably to collagen type IV and fibronectin. TGF.beta.1 enhanced adhesion. Again, these effects were less pronounced in the FTC **metastases**. In conclusion, TGF.beta.1 inhibits the growth, migration, and invasion of thyroid cancer cell in vitro. It

enhances adhesion to components of the extracellular matrix. Metastatic thyroid tumors may be less responsive to the neg. regulation of TGF.beta.1.

L57 ANSWER 40 OF 42 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1997:311310 BIOSIS
DOCUMENT NUMBER: PREV199799619113
TITLE: CD44 and its v6 spliced variant in lung tumors: A role in histogenesis.
AUTHOR(S): Fasano, Maria; Sabatini, Maria T.; Wieczorek, Rosemary; Sidhu, Gurdip; Goswami, Sunanda; Jagirdar, Jaishree [Reprint author]
CORPORATE SOURCE: Dep. Pathol. 4W1, Bellevue Hosp., 27th and 1st Ave., New York, NY 10016, USA
SOURCE: Cancer, (1997) Vol. 80, No. 1, pp. 34-41.
CODEN: CANCAR. ISSN: 0008-543X.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 26 Jul 1997
Last Updated on STN: 26 Jul 1997

AB BACKGROUND. CD44 is a polymorphic family of cell surface glycoproteins with a variety of functions including participation in **cell adhesion** and migration as well as modulation of cell-matrix interactions. Expression of the standard form of CD44 (CD44s) and its variant isoforms has been shown in both normal and neoplastic tissue and holds promise as a prognostic indicator. METHODS. The authors investigated the expression of CD44s and its v6 isoform (CD44v6) immunohistochemically in 7 fetal lungs (gestational age between 11-36 weeks) and in 80 lung tumors of various histologic types, degrees of differentiation, and clinical stages. RESULTS. In the fetal lung, CD44v6 was expressed as membranous and luminal staining of epithelial cells throughout gestation and basal staining of bronchial epithelium late in gestation. Nonneoplastic adult lung showed CD44v6 expression that was restricted to epithelial cells with **membranous** staining of **basal** bronchial cells and squamous metaplasia as well as basolateral membranous staining of type 2 pneumocytes. CD44s showed similar but less intense staining and was in addition present on lymphocytes and macrophages. Tumorlets and neuroepithelial bodies were CD44v6 negative. Nearly all squamous cell carcinomas (97%) were positive for CD44v6 with patterns similar to squamous metaplasia and with more intense staining at the periphery of tumor nests. Most adenocarcinomas (90%) were CD44v6 negative whereas most bronchioloalveolar cell carcinomas (71%) were CD44v6 positive with patterns similar to that in type 2 pneumocytes. Most large cell carcinomas (71%), carcinoid tumors (67%), and all small cell carcinomas were CD44v6 negative. CD44v6 expression did not correlate with clinical stage. CD44v6 expression in lymph node **metastases** was identical to that of the primary tumor. CONCLUSIONS. The results of the current study show that CD44v6 is localized differently in fetal and adult lung, suggesting a difference in function. In the fetal lung, it may modulate growth factors important in morphogenesis and maturation. In the adult nonneoplastic lung, CD44v6 is associated with stem cells, namely basal cells and type 2 pneumocytes, and may act to anchor these cells to the matrix and be important in migration during repair or neoplasia. In addition, CD44v6 expression is maintained throughout tumorigenesis in squamous cell carcinoma and bronchioloalveolar cell carcinoma, suggesting a histogenetic relationship between the stem cells and the respective tumors. Conversely, most neuroendocrine tumors

and the cells of the dispersive neuroendocrine system do not express CD44v6, implying a separate histogenetic lineage in these tumors.

L57 ANSWER 41 OF 42 WPIX COPYRIGHT 2003 THOMSON DERWENT on STN
ACCESSION NUMBER: 1998-017638 [02] WPIX
CROSS REFERENCE: 1996-077339 [08]; 1999-105124 [09]; 1999-601297 [51]
DOC. NO. CPI: C1998-006485
TITLE: Inhibiting **basal** lamina **membrane** formation by animal cells or tissue - by type-IV collagen polypeptides selected from NC1 and 7S domains, useful in, e.g. inhibiting angiogenic invasion of tissue.
DERWENT CLASS: B04 D16
INVENTOR(S): HUDSON, B G; SARRAS, M P
PATENT ASSIGNEE(S): (UNIV) UNIV KANSAS MEDICAL CENT
COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
US 5691182	A	19971125	(199802)*		17

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
US 5691182	A	CIP of	US 1994-268969	19940630
			US 1995-497206	19950630

PRIORITY APPLN. INFO: US 1995-497206 19950630; US 1994-268969 19940630
AB US 5691182 A UPAB: 20020424
Inhibiting **basal** lamina **membrane** (BLM) formation by animal cells or tissue, comprises: (a) contacting the cells or tissue with a polypeptide composition, where the composition comprises at least 1 domain of type IV collagen selected from NC1 and 7S domains. Also claimed are: (1) a method for cultivation of animal cells in vitro performed analogically to the above method, to disrupt the formation of BLM contacts between the cells and the extracellular matrix; (2) a method for disrupting basal lamina contact formation between animal cells or tissues and basal lamina performed analogically to method (1) , and (3) a method for inhibiting angiogenesis in animal tissue performed analogically to method (1).

USE - The methods are used to manipulate intracellular and intertissue interactions. The methods can inhibit **metastasis**, angiogenesis, angiogenic invasion of tissue and lymphocyte adhesion and mobility. The methods can also control cell division, reduce scar tissue formation, complications due to **cell adhesion** in organ transplants, intervene in epithelial tissue formation and maintain pluripotent cell isolates in vitro while inhibiting morphological changes and differentiation.
Dwg.0/10

L57 ANSWER 42 OF 42 WPIX COPYRIGHT 2003 THOMSON DERWENT on STN
ACCESSION NUMBER: 1996-077339 [08] WPIX
CROSS REFERENCE: 1998-017638 [02]; 1999-105124 [09]; 1999-601297 [51]
DOC. NO. CPI: C1996-025576

TITLE: Use of isolated domains of type IV collagen - for inhibiting **basal** lamina **membrane** formation in cell or tissue development.
DERWENT CLASS: B04 D16
INVENTOR(S): HUDSON, B G; SARRAS, M P
PATENT ASSIGNEE(S): (UNIV) UNIV KANSAS MEDICAL CENT
COUNTRY COUNT: 65
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9600582	A1	19960111	(199608)*	EN	37
RW: AT BE CH DE DK ES FR GB GR IE IT KE LU MC MW NL OA PT SD SE SZ UG					
W: AM AT AU BB BG BR BY CA CH CN CZ DE DK EE ES FI GB GE HU IS JP KE KG KP KR KZ LK LR LT LU LV MD MG MN MW MX NO NZ PL PT RO RU SD SE SG SI SK TJ TM TT UA UG US UZ VN					
AU 9530008	A	19960125	(199617)		
US 5567609	A	19961022	(199648)		12
EP 767676	A1	19970416	(199720)	EN	
R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE					
EP 1129721	A2	20010905	(200151)	EN	
R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE					
EP 767676	B1	20011121	(200176)	EN	
R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE					
DE 69524094	E	20020103	(200210)		
ES 2164160	T3	20020216	(200222)		
US 6384012	B1	20020507	(200235)		
US 6419924	B1	20020716	(200248)		
US 6448222	B1	20020910	(200263)		
US 2003013194	A1	20030116	(200308)#		

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
WO 9600582	A1		WO 1995-US8299	19950630
AU 9530008	A		AU 1995-30008	19950630
US 5567609	A		US 1994-268969	19940630
EP 767676	A1		EP 1995-926149	19950630
			WO 1995-US8299	19950630
EP 1129721	A2	Div ex	EP 1995-926149	19950630
			EP 2001-108470	19950630
EP 767676	B1		EP 1995-926149	19950630
			WO 1995-US8299	19950630
		Related to	EP 2001-108470	19950630
DE 69524094	E		DE 1995-624094	19950630
			EP 1995-926149	19950630
			WO 1995-US8299	19950630
ES 2164160	T3		EP 1995-926149	19950630
US 6384012	B1	Cont of	US 1994-268969	19940630
		Cont of	US 1995-497206	19950630
		Cont of	US 1997-800965	19970218
			US 1998-183548	19981030
US 6419924	B1	Cont of	US 1994-268969	19940630
		Cont of	US 1995-497206	19950630
		Cont of	US 1997-800965	19970218
		Cont of	US 1998-183548	19981030

			US 2000-723602	20001128
US 6448222	B1	Cont of	US 1994-268969	19940630
		Cont of	US 1995-497206	19950630
		Cont of	US 1997-800956	19970218
		Cont of	US 1998-183548	19981030
			US 2000-723791	20001128
US 2003013194	A1	Cont of	US 2000-723791	20001128
			US 2002-139946	20020506

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 9530008	A	Based on	WO 9600582
EP 767676	A1	Based on	WO 9600582
EP 1129721	A2	Div ex	EP 767676
EP 767676	B1	Related to	EP 1129721
		Based on	WO 9600582
DE 69524094	E	Based on	EP 767676
		Based on	WO 9600582
ES 2164160	T3	Based on	EP 767676
US 6384012	B1	Cont of	US 5567609
		Cont of	US 5691182
		Cont of	US 5856184
US 6419924	B1	Cont of	US 5567609
		Cont of	US 5691182
		Cont of	US 5856184
		Cont of	US 6384012
US 6448222	B1	Cont of	US 5567609
		Cont of	US 5691182
		Cont of	US 5856184
		Cont of	US 6384012
US 2003013194	A1	Cont of	US 6448222

PRIORITY APPLN. INFO: US 1994-268969 19940630; US 1995-497206 19950630; US 1997-800965 19970218; US 1998-183548 19981030; US 2000-723602 20001128; US 1997-800956 19970218; US 2000-723791 20001128; US 2002-139946 20020506

AB WO 9600582 A UPAB: 20030204

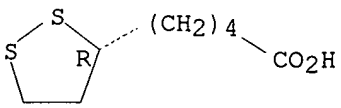
The following are claimed: (A) a method for inhibiting **basal** lamina **membrane** formation in cell or tissue development comprises contacting the cell or tissue with at least 1 isolated domains of type IV collagen; (B) a method for in vitro cultivation of cells comprises contacting the cells to be cultivated with an isolated domain of type IV collagen to disrupt the formation of **basal** lamina **membrane** or extracellular matrix contacts; (C) a method for disrupting basal lamina contact formation with cells or tissues comprises contacting the cells or tissues with an isolated domain of type IV collagen; and (D) a method for inhibiting angiogenesis in tissue comprises contacting the tissue with at least 1 isolated domains of type IV collagen.

USE - The methods can be used for e.g. inhibition of **metastasis**, control of cell division, redn. of scar tissue formation, intervention in epithelial tissue formation, inhibition of angiogenesis, redn. of complications due to **cell adhesion** in organ transplants, inhibition of angiogenic invasion

of tissue or the inhibition of lymphocyte adhesion and mobility. They can also be used for the in vitro manipulation of cells and tissues, e.g. in maintaining cell cultures in undifferentiated or homeostatic states, non-enzymatic dispersal of cells from attachments or the maintenance of confluent cells in suspensions for propagation, maintenance or collection. Dwg.0/10

L1 ANSWER 2 OF 2 REGISTRY COPYRIGHT 2002 ACS
RN 1200-22-2 REGISTRY
CN 1,2-Dithiolane-3-pentanoic acid, (3R)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 1,2-Dithiolane-3-pentanoic acid, (R)-
CN 1,2-Dithiolane-3-valeric acid, (+)- (8CI)
OTHER NAMES:
CN (R)-(+)-.alpha.-Lipoic acid
CN (R)-.alpha.-Lipoic acid
CN (R)-Lipoic acid
CN .alpha.-(+)-Lipoic acid
CN .alpha.-Lipoic acid
CN d-Thioctic acid
CN **Lipoic acid**
CN R-(+)-Thioctic acid
FS STEREOSEARCH
MF C8 H14 O2 S2
CI COM
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CAPLUS, CASREACT, CEN, CHEMCATS, CHEMINFORMRX, CHEMLIST, CIN, CSCHEM, DIOGENES, DRUGNL, DRUGUPDATES, EMBASE, HODOC*, IFICDB, IFIUDB, IPA, MEDLINE, MRCK*, NAPRALERT, PROMT, TOXCENTER, TOXLIT, USPATFULL
(*File contains numerically searchable property data)

Absolute stereochemistry. Rotation (+).



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

511 REFERENCES IN FILE CA (1967 TO DATE)
40 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
516 REFERENCES IN FILE CAPLUS (1967 TO DATE)

=> file caplus

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	9.38	9.53

FILE 'CAPLUS' ENTERED AT 15:32:53 ON 13 FEB 2002

FILE COVERS 1907 - 13 Feb 2002 VOL 136 ISS 7
FILE LAST UPDATED: 12 Feb 2002 (20020212/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.